Prolotherapy and Platelet Rich Plasma Therapy: Separating Fact from Fiction

Brian Sokalsky, DO
Jersey Shore Sports Medicine

Objectives

• Define Prolotherapy and Platelet-Rich Plasma Injection
• Understand the pathophysiology of the healing effects of these treatments
• Understand the types of chronic injuries that can be treated with prolotherapy and platelet-rich plasma injections

Science
What is Prolotherapy

• Prolotherapy is the injection of a substance stimulating the body’s natural healing response to treat an injured joint or connective tissue
• Traditionally, the most common substance used is dextrose
• PRP and stem cell treatments fall into the category of prolotherapy

What is PRP?

• A type of prolotherapy utilizing the patient’s own blood as the irritant
• A volume of plasma that has a platelet count above the baseline of whole blood
  – Some early articles quoted higher concentrations

How is PRP Prepared?

• Gravitation Platelet Sequestration (GPS)
  – Tabletop centrifuge system
  – Blood drawn from patient
    • Amount based on system used, injury treated, concentration of platelets
    • Anti-coagulant added
      – Anticoagulant Citrate Dextrose-A (ACD-A)
  – Centrifuge
    • Single spin vs double spin
    • Activation
  – Injection
    • Use of Ultrasound
    • What injuries?
How does PRP Work?

- **Platelets**
  - Cytoplasmic fragments of megakaryocytes
  - Formed in bone marrow
  - 150,000-350,000/uL on average
  - Lack nuclei but have other organelles
    - Alpha, gamma, delta granules
  - Granules contain more than 30 bioactive proteins
  - Primary function involves hemostasis

How does PRP/Prolo work?

- **Healing-3 stages**
  - Inflammation
  - Proliferation
  - Remodeling

How does PRP work?

- **Tissue injury activates inflammatory phase**
  - Bioactive proteins begin to be released within 10 minutes of clot initiation
    - 95% released within an hour
    - Additional factors can last for the remaining several days of the platelets’ life span
  - Interaction of growth factors and surface receptors on target cells trigger regeneration process
    - Cellular proliferation
    - Matrix formation
    - Osteoid production
    - Collagen synthesis
How do PRP/Prolo work?

### Growth Factors

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Effects</th>
</tr>
</thead>
</table>
| PDGF          | • Macrophage activation and angiogenesis  
                • Fibroblast chemotaxis and proliferation  
                • Enhances collagen synthesis  
                • Enhances the proliferation of bone cells |
| TGF-B         | • Enhances the proliferative activity of fibroblasts  
                • Stimulates biosynthesis of Type I collagen and fibronectin  
                • Induces deposition of bone matrix  
                • Inhibits osteoclast formation and bone resorption |
| IGF-I         | • Chemotactic for fibroblasts and stimulates protein synthesis  
                • Enhances bone formation by proliferation and differentiation of osteoblasts |
| PDEGF         | • Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts |
| PDGF          | • Induces vascularization by stimulating vascular epithelial cells |
| PF-4          | • Stimulates the initial influx of neutrophils into wound  
                • A chemoattractant for fibroblasts  
                • A potent ant-heparin agent |
| EGF           | • Cellular proliferation  
                • Differentiation of epithelial cells |
| VEGF          | • Angiogenesis  
                • Migration and mitosis of endothelial cells  
                • Creation of blood vessel lumen  
                • Creates fenestrations  
                • Chemotactic for macrophages and granulocytes  
                • Vasodilation (indirectly by release of NO) |

### PRP Preparation Variables

- Platelet concentration  
  - Too high/too low?  
- WBCs/RBCs  
- Activation  
- Lidocaine  
- Number of injections.spacing  
- Use of NSAIDs/Supplements/Ice
Is PRP FDA Approved?

• Yes, sort of...
  – PRP devices have a 510(k) clearance
    • Low risk, substantially equivalent to previously cleared device
    • No clinical data required
  – Devices only cleared for using PRP intraoperatively with bone graft material
    • All other uses considered off label
  – Brewing controversy-FDA regulating HCT/P
    • “Less than minimally manipulated” don’t require PMA
      – Stem cells/Regenokine (Kobe Bryant)

Do They Work?!?

• Lateral Epicondylitis
  – Gosens T, Peerbooms J, et al
    • PRP > Corticosteroids over 2 years in pain and function
  – Mishra A, Skrebnik N, et al
    • PRP > Control at 24 weeks
      – No difference at 12 weeks
  – Krogh T, Fredberg U, et al
    • No significant difference at 3 months between PRP, corticosteroid and saline
      – Lost too many patients to report findings past 3 mos
    • Strong evidence PRP injections no efficacious
    • Rebuttal letter refuting conclusion

Do They Work?!?

• Lateral Epicondylitis
  – Rabago D, Best TM, et al
    • Strong evidence supporting prolotherapy, PRP, polidocanol, autologous whole blood
      – Need for better studies
  – Scarpone M, Rabago D, et al
    • Prolotherapy > controls at 1 yr
Do They Work?!?

• Knee OA
  – Halpern B, Chaudhry S, et al
    • Decreased pain, increased function at 1 yr with PRP
      – No change in MRI
    • Prospective cohort study, 1 injection
  – Patel S, Dhillon M
    • Decreased pain and stiffness, improved function at 6 mos
      – Single or 2 injection series equal—both better than saline
      – Randomized control trial

Do They Work?!?

• Knee OA-in vitro
  – Osterman C, McCarthy MB, et al
    • 2 PRP systems: high vs low platelet/WBC concen
    • Both had equal anti-inflam effect on cartilage, synovium and gene expression
    • PRP and HA suppress inflam mediators and gene expression in cartilage and synoviocytes vs control
    • PRP>HA and control for MMP-13 redux and HAS-2 expression→better endogenous HA production and decreased catabolism

Do They Work?!?

• Knee OA-in vitro
  – Braun H, Kim HJ, et al
    • LR-PRP vs LP-PRP
    • LP-PRP: elevated TNF-alpha, decreased IL-1B and IL-6
      – LR-PRP results in increased cell death and pro-inflam
  – Kisiday J, McIlwraith CW
    • Equine cartilage
    • Single spin vs double spin
    • Double spin-inc WBCs and catabolic gene expression
Do They Work?!?

- **Rotator Cuff Tendinopathy**
  - Kesikburun S, Tan AK, et al
    - Double blind randomized trial-PRP vs placebo
    - No difference in pain and function at 1 year
      - Both showed significant improvement
    - In vitro RTC tenocytes with degen tears
    - 14 day culture-increased gene expression, cell proliferation and synthesis of tendon matrix

Do They Work?!?

- **Achilles Tendinopathy**
  - de Jonge S, de Vos RJ, et al
    - Randomized controlled trial-PRP vs saline; both with eccentric program
    - No difference at 1 year follow up
      - Both showed significant improvement
  - de Vos RJ, Weir A, et al
    - Randomized control trial-PRP vs saline; both with eccentric program
    - No difference at 6 months

Do They Work?!?

- **Achilles Tendinopathy**
  - Boesen A, Boesen M, et al
    - Randomized control trial-PRP vs HVI vs Placebo
      - All received eccentric program
    - HVI and PRP significant decrease in pain, function and tendon thickness
  - Yelland M, Sweeting K
    - Randomized control trial-PRP vs eccentrics vs both
      - Prolo and combined therapy had more rapid improvements in pain and function
      - At 1 year, combined therapy had significantly decreased pain
Do They Work?!?

• Patella Tendinopathy
  — Charousset C, Zaoui A, et al
    • Case series-series of 3 weekly PRP injections
      — All cases failed nonoperative treatments
    • Significant improvement in pain and function
      — 21 of 28 returned to pre-symptom sporting level (professional or semi-pro)
  — Vetrano M, Castorina A, et al
    • Randomized control trial-2 PRP injections vs 3 ECST tx
    • PRP better pain and function at 6 months and 1 year
      — Equal at 2 months

Do They Work?!?

• Patella Tendinopathy
  — Ryan M, Wong A, et al
    • Case series-Prolo until satisfied with treatment
      — All failed nonoperative tx prior to start
    • Mean of 4 sessions (+/-3)-improvement in VAS scores at rest, ADL's and sports at 45 week follow up

Do They Work?!?

• Patella Tendinopathy-Reviews
  — Liddle A, Rodriguez-Merchan EC
    • Case studies-decrease pain and increase function
    • Comparison studies-inconclusive
  — Andia I, Maffulli N
    • No definitive conclusions, but...
      — Mostly positive outcomes
      — Reasonable before considering surgical treatments
      — Best formulation, number of injections or what phase to use it is unclear
Do They Work

- Hamstring injuries
  - Hamid MSA, Ali MRM, et al
    - Randomized control trial-PRP+PT vs PT in grade 2 injury
    - Significantly earlier RTP in PRP vs controls

Do They Work?!?

- Chronic Tendinopathy-Harmon K, Drezner J, Rao A

<table>
<thead>
<tr>
<th></th>
<th>AB</th>
<th>LR-PRP</th>
<th>LP-PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>10</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>Avg symptom duration (mos)</td>
<td>12.3</td>
<td>35.8</td>
<td>37.6</td>
</tr>
<tr>
<td>Avg VAS improvement</td>
<td>15.2</td>
<td>21.8</td>
<td>25</td>
</tr>
<tr>
<td>Percent of VAS improve &gt;20 points</td>
<td>40%</td>
<td>62%</td>
<td>83%</td>
</tr>
</tbody>
</table>

CASES
Lateral Epicondylosis

• DW
  – 59 y/o male with 10 years intermittent lateral elbow pain
  – Recent flare up last few months - no injury
  – 1 cort inj 10 years ago with initial relief
  – Avid golfer
  – Failed another cort inj and PT
  – 1 PRP injection with significant pain relief at 8 weeks

Achilles Tendinosis

• EH-53 y/o male with pain for 18 months
  – No injury - was running 60-70 mi/wk
  – Failed eccentric program
  – Law enforcement ➔ no surgery
  – Wants to continue running
  – No pain at 10 week follow up

Trochanteric Bursitis

• DK-65 y/o female with lat hip and thigh pain for 28 months
  – Original injury when reaching for tennis shot
  – Extensive tx including NSAIDs, multiple corticosteroid injections, PT, ART all with temporary relief
  – Constant pain and limited playing tennis
  – Injection + continued PT and ART
  – Pain free at 12 weeks
Partial Plantar Fascia Rupture

- RC-42 y/o male with foot pain x 1yr
  - Partial rupture while running
  - Active in Crossfit-limited by foot pain
  - Failed NSAIDs and PT-recommended to have surgery
  - One injection-minimal pain at 10 weeks, able to return to Crossfit
  - Less success with medial epicondylitis

Grade 2 Hamstring Tear

- LH-72 y/o with injury to proximal hamstring tendon
  - Unknown injury
  - Pain for 6 months
  - MRI confirmation of injury
  - Avid golfer-limited by injury
  - Pain free 72 hours after injection-return to golf without limitations in 2 weeks (continued PT)
  - Similar injury contralat hamstring 6 mos later leading up to Middle East golf trip
    - PRP prior to trip-pain free for trip

Hip Labral Tear

- AC-40 y/o female with hip labral tear
  - Pain for years, worse for last 9 months since starting Crossfit
  - Failed meds and PT
  - Runs a nursery school-unable to get surgery
  - Eager to return to exercising-gaining weight
  - PRP injection-pain free at 12 weeks
    - Hasn’t restarted exercising due to unrelated foot injury
Questions?