Conflicts of Interest

- I have no conflicts of interest regarding this presentation
PLATELET RICH PLASMA: AN UPDATE WHERE ARE WE NOW?

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Advanced Orthopaedic Specialists
Goals

- Background
  - Healing Response
- The Basic Science
- Uses
- Evidence Based
- Summary
Goals

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What is PRP (Platelet Rich Plasma)?
- Biologic, “regenerative biomedicine”
- Concentrated platelets
  - Ideally 3-8X
- Processed from autologous, whole blood
- Provides “Supra-physiologic” concentrations of growth factors

No universal definition of what constitutes PRP vs PPP

Ideal concentration is opinion based
Background

How is it made?
- Centrifuged whole blood
- Coagulation inhibitors may be used
  - Previous issues with bovine inhibitors
- Platelet activators may be used
- Volume produced depends on which system used
- Applied in either
  - Injectable form
  - Solid, matrix form
### Background

<table>
<thead>
<tr>
<th>System</th>
<th>Platelet Conc.</th>
<th>Activator</th>
<th>Centrifuge time</th>
<th>Leukocytes</th>
<th>Blood Volume needed (ml)</th>
<th>PRP volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrex ACP</td>
<td>2-3X</td>
<td>No (use within 30 minutes)</td>
<td>1, 5 min step</td>
<td>No</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Biomet GPS III</td>
<td>3-8x</td>
<td>Autologous thrombin and calcium chloride</td>
<td>1, 15 minute step</td>
<td>Yes</td>
<td>27-110</td>
<td>3-12</td>
</tr>
<tr>
<td>Cascade</td>
<td>1-1.5x</td>
<td>Calcium chloride</td>
<td>1, 6 minute for PRP</td>
<td>No</td>
<td>9-18</td>
<td>4-9</td>
</tr>
<tr>
<td>SmartPReP2</td>
<td>4-6x</td>
<td>Bovine thrombin or calcium</td>
<td>2, 14 minute step</td>
<td>Yes</td>
<td>20-120</td>
<td>3-20</td>
</tr>
<tr>
<td>PRGF</td>
<td>2-3x</td>
<td>Calcium chloride</td>
<td>1, 8 minute step</td>
<td>No</td>
<td>9-72</td>
<td>4-32</td>
</tr>
<tr>
<td>Magellan</td>
<td>3-7x</td>
<td>Calcium chloride</td>
<td>2, 4-6 minute steps</td>
<td>Yes</td>
<td>30-60</td>
<td>6</td>
</tr>
</tbody>
</table>
Goals

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Background: The Healing Response

- **Inflammatory phase**
  - First week after injury
    - Hemostasis $\rightarrow$ recruitment of macrophages and fibroblasts

- **Proliferative phase**
  - Within first 2 days to 2 weeks
    - Formation of extra-cellular scaffold

- **Maturation/remodeling phase**
  - Up to first year
    - Type 1 collagen replacing scaffold
Background: The Healing Response

- Growth factors
  - IGF-1 → early inflammatory phase
    - Enhances collagen and matrix synthesis
  - TGF-B → pro-inflammatory
    - Enhances matrix and collagen synthesis, angiogenesis
  - PDGF → facilitates proliferation of other growth factors
    - Attracts stem cells and contributes to remodeling
Background: The Healing Response

 Growth factors
  • VEGF → peaks after inflammatory phase
    ○ Promotes angiogenesis and neovascularization
  • b-FGF → angiogenesis, cell migration, creates collagenase, production of granulation tissue
Background: The Healing Response

What does PRP bring to the healing table?

- Alpha granules
  - The storage packets of growth factors
  - Each platelet contains 50-80 granules
  - The de-granulation releases the growth factors needed to augment healing
Background: The Healing Response

- **Alpha granules**
  - Theory that activators will increase degranulation
    - Reason why some systems include external activators
  - Some studies show injured collagen fibers will stimulate de-granulation as well
Goals

 Background
  • Healing Response
 The Basic Science
 Uses
  • Limit to Muscle, Tendon, Ligament
 Evidence Based
 Summary
The Basic Science

- **Horse tendons**
  - Schnabel et al.
  - Culture in PRP vs other blood products
  - Higher anabolic gene expression in PRP

- **Human tenocytes**
  - de Mos et al.
  - PRP vs. PPP
    - PRP increase in matrix degrading enzymes (faster recovery)
The Basic Science

- Rabbit skeletal muscle stem cells
  - Gates et al.
  - Increased expression of myogenic activity

- Mesenchymal stem cells
  - Mishra et al.
  - Buffered in PRP, increased proliferation
Goals

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Uses: Muscle

  - Animal study (rats)
  - Tibialis anterior strain
    - large strain vs small strain
  - PRP shortened healing by 14-21 days in small strain group
  - Little change in large strain group
Uses: Tendon

- Lots of studies
  - Lateral epicondylitis
  - Patellar tendinopathy
  - Achilles tendinopathy
  - Rotator Cuff tendinopathy
**Uses: Lateral Epicondylitis**

<table>
<thead>
<tr>
<th>Study (y)</th>
<th>Study Design</th>
<th>Human or Animal</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Control Group</th>
<th>Details</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra &amp; Paveiko 2005 (53)</td>
<td>Prospective, cohort study</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>PRP injection (N = 16)</td>
<td>Local anesthetic injections (N = 5)</td>
<td>Chronic, mean of 15 mo of pain, refractory, considering surgery</td>
<td>VAS</td>
<td>PRP group: 60% improvement in pain scores at 8 wk, 81% at 6 mo, &amp; 93% at follow-up longer than 1 y out. 73% success rate in the PRP group, 49% in the corticosteroid group. PRP group progressively improved; the steroid group regressed. 1. 79% of the patients had significant or complete relief of pain even with strenuous activity. 2. Average pain and Nirschl stage scores decreased. 3. 9 patients had additional injections and had greater improvement in Nirschl scores.</td>
</tr>
<tr>
<td>Peetooms et al 2010 (54)</td>
<td>Randomized controlled trial</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>PRP injection (N = 51)</td>
<td>Corticosteroid Injection (N = 49)</td>
<td>Chronic, more than 6 mo of pain; peppering technique was used</td>
<td>VAS, DASH score</td>
<td></td>
</tr>
<tr>
<td>Edwards &amp; Calandrauco 2003 (55)</td>
<td>Prospective, case series</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>ABIs (N = 28)</td>
<td>—</td>
<td>At least 3 mo, conservative management failed</td>
<td>VAS, Nirschl stage scores</td>
<td></td>
</tr>
<tr>
<td>Suresh et al 2006 (42)</td>
<td>Prospective, case series</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>ABIs (N = 20)</td>
<td>—</td>
<td>Chronic, refractory, 12 mo symptomatic; dry needing was used</td>
<td>VAS scores, modified Nirschl scores, ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Connell et al 2006 (56)</td>
<td>Prospective, case series</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>ABIs (N = 35)</td>
<td>—</td>
<td>Chronic, refractory (mean of 13.8 mo symptomatic)</td>
<td>VAS scores, Nirschl scores, ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Gani et al 2007 (57)</td>
<td>Prospective, case series</td>
<td>Human, nonsurgical</td>
<td>Lateral epicondylitis</td>
<td>ABIs (N = 26)</td>
<td>—</td>
<td>Chronic, refractory (over 6 mo duration of symptoms)</td>
<td>VAS scores, Nirschl scores</td>
<td></td>
</tr>
</tbody>
</table>

PRP = platelet-rich plasma; VAS = visual analog pain score; DASH = Disabilities of the Arm, Shoulder, and Hand score; ABI = autologous blood injection.
Uses: Lateral Epicondylitis

- Mishra and Pavelko (2006)
  - One of the most cited articles
  - Chronic, refractory lateral epicondylitis
  - 15 patients, failed conservative measures
  - Single PRP injection
    - control was bupivacaine
Uses: Lateral Epicondylitis

- Mishra and Pavelko (2006)
  - Measures VAS and Mayo elbow scores at 2, 6 and 25 months
  - Outcomes
    - 2 months → 60% vs 16% improvement (P=.001)
    - Final f/u → 93% reduction in pain, no complications
    - 60% of control group withdrew for other treatment
Uses: Lateral Epicondylitis

 Peerbooms et al (2010)
  - RCT, Level 1 data
    - Only true RCT to date
  - 100 patients (51 PRP:49 CSI)
  - 1 yr f/u
    - 73% success in PRP group
    - 49% in CSI group
## Uses: Patellar Tendinopathy

| Study (y)       | Study Design                      | Human or Animal | Diagnosis                                      | Intervention | Control Group                     | Details                                                                 | Outcome Measures                                      | Results                                                                                                                                 |
|-----------------|-----------------------------------|-----------------|------------------------------------------------|--------------|------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Filardo et al.  | Prospective, nonrandomized, controlled trial | Human, nonsurgical | Chronic refractory patellar tendinopathy | PRP injections, 2 wk apart + PT (N = 15) | PT only (N = 16) | The PRP group had a longer duration of symptoms. 150 mL of venous blood was extracted to produce 20 mL of PRP. 5 mL was injected within 2 h, remaining aliquots were stored at −30°C and injected at 16-d intervals; the platelet concentration was 6 times higher than that in whole blood. | Tegner, EQ VAS scores, pain level, complications, functional recovery, & patient satisfaction | 1. PRP group improved in all measuremetn scores. 2. PRP group further improved at 6-mo follow-up after physical therapy was incorporated. 3. A higher improvement in sports activity was found in the PRP group. |
| Kon et al.      | Prospective, pilot study          | Human, nonsurgical | Chronic patellar tendinosis                  | 3 consecutive PRP injections (15 d apart) (N = 20) | —                          | Mean of 20.7 mo of pain                                                  | EQ VAS score, Tegner score                               | Complete or significant improvement in 70% of patients at 6 mo. 85% were satisfied with the results. 1. Improved scores, reduction in intensity, tenderness, thickness, & tendinosis area. 2. Patients returned to sports after about 14 mo after treatment. |
| James et al.    | Prospective cohort study          | Human, nonsurgical | Chronic patellar tendinosis                  | Autologous blood injection (N = 47) | —                          | Mean of 12.9 mo symptomatic                                              | VISA, ultrasonography                                    | 1. In the earlier phase, the PRP group had a 72% increase in force to failure, 39% increase in ultimate stress, & 53% increase in stiffness compared w/ controls. 2. There was no statistical difference in the later stage. 3. In weekly histologic analyses, better healing was seen in the PRP group, w/ greater neovascularisation in the first 2 wk & w/ more dense & mature tissue at wk 3. |
| Lyos et al.     | Controlled animal study           | Rabbit model     | Patellar tendon defect                       | PRP treatment (N = 20) | Surgical defect w/ no PRP treatment (N = 20) | PRP gel administered on surgically induced patellar tendon mid-portion resections | Mechanical properties & histology of the regenerated tendon were assessed after 14 & 28 d | 1. At 3 & 7 of after injury, cell proliferation of circulation-derived cells was 2 times higher in the PRP group compared with a control group (no PRP). 2. Early phase: immunoreactivity of types I & II collagen was higher in the PRP group. |
| Kajiwara et al. | Controlled laboratory animal study | Chimeric rats    | Patellar tendon injury                       | PRP injection | No PRP injection                   | Studied PRP in the activation of circulation-derived cells after patellar tendon injury in chimeric rats expressing a green fluorescent protein in the bone marrow and in circulating cells | Cellular quantification, measurement of immunoreactivity for types I & III collagen | 1. At 3 & 7 of after injury, cell proliferation of circulation-derived cells was 2 times higher in the PRP group compared with a control group (no PRP). 2. Early phase: immunoreactivity of types I & II collagen was higher in the PRP group. |
Uses: Patellar Tendinopathy

- Human Data is limited
- Filardo et al (2010)
  - Non-RCT, N=31
  - Serial PRP + PT (15) vs. PT alone (16)
  - 3 PRP, 2 weeks apart with eccentric strengthening
  - PRP group
    - Improved in all measures
    - Continued to improve at 6 months
    - Higher improvement in sports activity
Uses: Patellar Tendinopathy

- Kon et al (2009)
  - Prospective, pilot study (no control)
  - 3 PRP injections, 15 days apart
  - 6 month f/u
    - 70% stated complete or significant improvement
    - 80% satisfied with results
Uses: Achilles Tendinopathy

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<tbody>
<tr>
<td>de Vos et al (2010)</td>
<td>Stratified, block-randomized controlled trial</td>
<td>Human, nonsurgical</td>
<td>Chronic mid-portion Achilles tendinopathy</td>
<td>PRP injection</td>
<td>Saline solution injection</td>
<td>Treated with eccentric exercises &amp; PRP injections or saline solution injections</td>
<td>VISA-A questionnaire</td>
<td>1. Both groups improved, &amp; they did not find significant differences between the groups</td>
</tr>
<tr>
<td>Sanchez et al (2007)</td>
<td>Case-control study</td>
<td>Human, surgical</td>
<td>Achilles tendon tear</td>
<td>PRGF (N = 6)</td>
<td>Conventional surgery</td>
<td>12 athletes had open suture repair after complete Achilles tendon tear; 6 athletes received a 4 mL, calcium PRGF injected intraoperatively within the tendon fibers after suturing; platelet-rich fibrin matrix was used to cover the site before closure of the skin; retrospectively compared with a matched conventional surgery group; allofibrin was given in the postoperative period</td>
<td>Range of motion, functional recovery, complications, ultrasonography, laboratory analysis</td>
<td>1. Platelet-rich treatment &amp; surgery: earlier recovery of range of motion (by about 4 wk); quicker return to training &amp; light running (difference of about 7 wk); less increase in cross-sectional area of the PRGF tendon on ultrasound</td>
</tr>
<tr>
<td>Aspenberg et al (2004)</td>
<td>Animal study</td>
<td>Rat model</td>
<td>Transected Achilles tendon</td>
<td>Platelet concentrate injection</td>
<td>—</td>
<td>PTP injected into rat transected Achilles tendons</td>
<td>Mechanical properties &amp; histology</td>
<td>1. 30% increase in tendon callus strength and stiffness after 1 wk</td>
</tr>
<tr>
<td>Vruchenko &amp; Aspenberg (2006)</td>
<td>Controlled animal study</td>
<td>Rat model</td>
<td>Transected Achilles tendon</td>
<td>A. Platelet gel or PRP injection in the Botox group (Botox) injections into the calf muscles for unloading, B. Mechanically stimulated in activity cages (increased physical activity) C. ± platelet gel D. ± Botox group</td>
<td>A. Saline solution buffer control injections in the Botox group, B. Ordinary cages, C. ± platelet gel, D. ± Botox group</td>
<td>Effects of platelets on Achilles tendon regeneration rats 3, 5, &amp; 14 d after transection</td>
<td>Tensile testing</td>
<td>1. At 2 wk, Botox group had reduced mechanical properties; in the early phases (d 3 and 5), PRP appeared to improve their mechanical properties of force, stiffness, &amp; area</td>
</tr>
</tbody>
</table>
2. Non-Botox group: PRP (gel & injection) increased stiffness & increased stress to failure |
3. Mechanical stimulation in isolation also appeared to increase force, energy uptake, and area but had no synergistic effect with platelet treatment |

Advanced Orthopaedic Specialists
Uses: Achilles Tendinopathy

- de Vos et al (2010)
  - Double blinded, placebo control, RCT
  - N=54, chronic Achilles tendinopathy
    - 2 months of symptoms
    - Excluded if had previous eccentric strengthening program
    - 27 PRP, 27 isotonic saline, US guidance used
Uses: Achilles Tendinopathy

- de Vos et al (2010)
  - Double blinded, placebo control, RCT
  - N=54, chronic Achilles tendinopathy
    - Both did 12 week supervised eccentric program
    - f/u at 6, 12, 24 weeks
      - Both groups improved, No difference found
      - Used bupivicaine for anesthetic
      - ? Inhibit effectiveness
Uses: Rotator Cuff

- Mostly as surgical repair adjuncts
- Studies have been +/-
  - Only one major prospective, Level 1 randomized research
    - No major difference in structural integrity compared with control
      - Repair with PRP vs repair without PRP
Uses: MCL

- No human studies
- Letson and Dahners (1994)
  - Rat MCL injury
    - Injected with PDGF
      - 73% (+/- 55%) stronger than contralateral controls
- Human results anecdotal
  - 2-3 weeks earlier than anticipated
Goals

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  - Limit to Muscle, Tendon, Ligament
- Evidence Based
- Summary
What does the evidence say?

- Increasing number of basic science and animal studies
- Paucity of human trials
  - No standardization of treatment
  - Anecdotally improves recovery by 2 weeks
- 1 vs. multiple injections
  - 1 seems to be effective, fenestration may help
  - The multiple injection “protocol” is without consistency
What does the evidence say?

- When is best time to administer in acute setting?
  - Chan et al
    - Better results at day 7 than day 3
    - At elite level, who waits 7 days?
What does the evidence say?

- **Exercise**
  - Early ROM can be helpful
  - Early light aerobic activity can be helpful
  - I begin eccentric strengthening program as early as tolerated
  - Goal is RTP by 3 weeks
What does the evidence say?

- **NSAIDs**
  - Most hold for minimum of 10 days prior
  - Not proven to inhibit, but possible
    - Don’t withhold ASA if cardio-protective

- **Ideal platelet concentration**
  - 600K-1mil per ml (no evidence for that)
What does the evidence say?

- WBC in preparation
  - Inhibit or help?
    - Help $\rightarrow$ anti-infective property
    - Inhibit $\rightarrow$ inhibitory effects on inflammatory mediators
What does the evidence say?

- Local anesthetics and corticosteroids
  - Carofino et al (2012)
    - Co-administration decreased PRP effectiveness
- External platelet activators
  - No consensus on if or when
What does the evidence say?

- MSK US guidance improves results
  - 0232T tracking CPT code
    - Includes imaging assisted guidance
    - I use it with every PRP
Where are we with PRP?
Summary

- Limited human research
- Tendon > Muscle > Ligament for now
- Limit NSAID use around the injection
- Don’t add local anesthetic
- Still more to learn
- Medicare tracking code now
- IOC had banned it in 2010, removed in 2011
References


- Engebretsen L, Steffen K et al. IOC consensus paper on the use of platelet-rich plasma in sports medicine. BJSM 2010;44:1072-81