PRP: Evidence and Use in Sports Medicine

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Director, Sports Medicine Fellowship
Team Physician, Wellesley College

Thank you for the invitation

Three Parts

- Part 1
  - Introduction and Basic science
- Part 2
  - Evidence base in sports medicine
- Part 3
  - Cases in sports medicine
THE BUZZ IS IN THE AIR…

Just prior to the kickoff of superbow XLIII, on field reporters from NBC credited Hines Ward’s rapid recovery with a knee sprain (MCL) to Platelet Rich Plasma therapy.

Takashi Saito, a star pitcher for the LA Dodgers suffered a tear of his ulnar collateral ligament.

Arthritis and PRP in the Boston Globe

Kay Lazar Boston Globe, Oct 19, 2009
PRP for Sports Injury in Baby Boomers

Boston Globe article 2011 February by Kay Lazar

IOC consensus paper on the use of platelet rich plasma in sports medicine


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"...proceed with caution in the use of PRP in athletic sporting injuries. We believe more work on the basic science needs to be undertaken...."

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What is regenerative bioinductive medicine?

- Regenerative biomedicine is emerging at the forefront of medicine
- As it relates to musculoskeletal and sports medicine, this includes
  - Prolotherapy and sclerosing agents
  - Extracorporeal shock wave therapy
  - Platelet rich plasma
  - Nitric oxide
  - Matrix metalloproteinase
  - Mesenchymal stem cells

Why is this important?

- Our basic science knowledge of sports injury has evolved.....
- We are no longer exclusively treating "itis"
- We are currently treating "opathy"
- We are trying to "regenerate", not "palliate"

DEFINITIONS & PATHOLOGY

- Ligament: attaches bone to bone
- Sprain: injury to ligament
- Enthesis: insertion site of tendon, ligament, fascia, or articular capsule into bone
- Enthesitis: inflammation of enthesis (common in rheumatologic disorders)
- Enthesopathy: any disorder of the enthesis
DEFINITIONS & PATHOLOGY

- The enthesis organ (Slobodin 2007):
  - Collection of related tissues at and near the enthesis (tendon and bone fibrocartilage, fat pads, bursae, synovium) which serve a common function of stress dissipation.

TENDON, LIGAMENT, ENTHESIS

Anatomy: Ligament and tendon attachments occur together

Normal Biologic Healing Response
MECHANISMS OF HEALING

● The Wound Healing Cascade: 3 Phases

● Inflammation Phase: Day 0-4 to 6
  ● Tissue injury activates COX-2 → vasodilation
  ● Growth factors (TGF-B, PDGF, PF4, LTB4, and IL-1) → attract macrophages and fibroblasts.

● Formation of ECM (Extracellular Matrix) by macrophages and fibroblasts

● Proliferation Phase: Day 4-14
  ● Fibroblasts differentiate into myofibroblasts which contract and close the wound (4).

● Maturation/Remodeling Phase: Day 8-1 yr
  ● TGF-β peaks from 7-14 days → controls collagen matrix formation.
  ● Type I collagen replaces proteoglycan and fibronectin → thicker and stronger matrix.
  ● Peak tensile strength reaches 70-80% of normal.
Role for Biologic Growth Factors (PRP) and Biologic Rational for their action

Platelet Rich Plasma (PRP)
- Autologous concentration of human platelets in a small volume of plasma
- Contains growth factors secreted by alpha granules of platelets
  - PDGFαα, PDGFββ, and PDGFαβ
  - TGFβ1 and TGFβ2
- Vascular endothelial growth factor
- Epithelial growth factor

Platelets: Not just for clotting anymore
- Platelets are the first cells to arrive at the site of injury
- Responsible for initiation of healing cascade
- α-granules and dense granules
PRP for Enthesopathy

- High concentration of growth factors / chemokines introduced into the non-healing area
- Starts the healing cascade
- Expect an inflammatory response
- Accelerates healing
- Appears to be direct correlation between # of platelets & tissue healing (TO A POINT!)
- Prefer 4-8X's normal

TREATMENT: PRP INJECTION

- Platelet-Rich Plasma (PRP) injection therapy:
  - Injection of autologous plasma rich in platelets and growth factors into dysfunctional tissues.
Activated Platelets Release Growth Factor Proteins into the Surrounding Tissue

The Measure of Available Platelets Relates to the Measure of Growth Factors at the Wound Site

Slide courtesy of Harvest technologies

Tissue Regeneration - Mechanism of Action

Cell Proliferation Requires the Interaction of Three Biological Elements:

- Scaffold
- Signal Proteins & Adhesion Molecules
- Undifferentiated Cells

Signal Proteins and Adhesion Molecules control:
1. Recruitment of cells to the scaffold
2. Cell division within the scaffold

Slide courtesy of Harvest technologies

PRP Human Studies in Musculoskeletal and Sports Medicine

- Bone
- Tendon
- Ligament
- Muscle
- Joint
- Arthritis
- Nerve
**PRP and Bone**

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**Mandibular Continuity Defects**

**Growth Factor Enhancement for Bone Grafts**

**Aim:** Prospectively evaluate the radiographic, histomorphic, and clinical effects of a PRP/autograft composite compared to autograft in mandibular continuity defects of at least 50 mm.

**Patient Groups:**
- Control (n=44) – Cancellous cellular marrow grafts
- Study (n=44) – PRP/autograft

**Results:**
- Addition of growth factors obtained by adding PRP to grafts:
  - At 2, 4, and 6 months, the grafts containing PRP showed a radiographic maturation rate approximately 2 times that of grafts without PRP.
  - Histomorphometric assessment revealed up to 30% greater bone density in PRP-enhanced grafts.


**Trabecular Bone Area at 6 Months**

**Non-PRP Enhanced Graft**

- Mean trabecular bone area is 55.1% ± 8%, p = 0.005
- Bone is partially woven (phase I) bone and partially lamellar bone (mature phase II bone)

**PRP Enhanced Graft**

- Mean trabecular bone area is 74.0% ± 11%, p = 0.005
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Mandibular Continuity Defects Growth Factor Enhancement for Bone Grafts

- Monoclonal antibody assessment of cancellous cellular marrow grafts demonstrated cells that were capable of responding to the growth factors by bearing cell membrane receptors.

Early Experience and Results of Bone Graft Enriched With Autologous Platelet Gel for Recalcitrant Nonunions of Lower Extremity

Chiu-Ching Chiang, MD; Chin-Tao Su, DDS; PGO; Ching-Kai Riang, MD; Wei-Ming Chen, MD.

Context:
Between anesthesia and efficacy of the graft, the treatment is comparable for orthopedic surgeons. The goal of this study was to assess the efficacy of the two types of bone grafts in mandible reconstruction.

Methods:
A total of 31 patients were included. All of them were treated with the bone grafting procedure with autologous platelet-enriched gel (PRP).

Findings:
The patients had a good response to the treatment with the platelet-enriched gel. The bone healing was observed to be improved in all cases.

PRP and Bone

- Plachokova et al.
- Systematic review of PRP on bone regeneration in dentistry
- "Found evidence for beneficial effects of PRP in the treatment of periodontal defects"

PRP: osteoinductive effect

- Sheep infraspinatus repair model using MRI scan and histology.
- Study demonstrated an increased formation of new bone and fibrocartilage at the healing site.

PRP and Muscle
Sanchez M, et al; “Application of Autologous Growth Factors on Skeletal Muscle Healing”, World Congress on Regenerative Medicine Podium Presentation, May 18, 2005

- Study: 20 patient prospective acute muscle injury pilot study with 6 month follow-up – Ultrasound guided injection of PRP.
  - Multiple, serial prp injections at one week intervals to defect sites after hematoma evacuation
  - Ultrasound demonstrated injured muscle healed fully without fibrosis. Functional capacities 50% faster than the control group.
  - The athletes had full recovery in half the expected times
PRP and Muscle

  - Pilot study
  - Professional athletes with muscle strain
  - Administered autologous conditioned serum
  - Control group received actovegin/traumeel
  - Found a reduction in recovery time in return to 100% activity in competitive sports. (16 days vs 22 days in the control group)
  - MRI recovery time was accelerated as well.

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PRP and Muscle

  - Tib anterior of rats injected with PRP or PPP for treatment of acute muscle strain (high repetition multiple small strains vs single large strain)
  - Conclusion: "local delivery of PRP can shorten recovery time after a muscle strain injury in a small animal model."
  - Recovery of muscle from a high repetition model has been shown to require myogenesis. This may explain why PRP was more effective in the high-repetition protocol.

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PRP and muscle

- Cugat: unpublished case series 2005
  - 14 professional athletes
  - 16 muscular injuries (soccer and basketball)
  - PRP injected under ultrasound after hematoma aspiration
  - 50% reduction in time to return to play in less severe injuries.
  - RTP diminished in each group according to severity
PRP and Tendon

Aim: IRB approved prospective pilot study to evaluate the efficacy of using PRP as a potential treatment for chronic severe epicondylar tendinosis.

Methods: 140 patients were evaluated for this study

- 20 patients (15%) met strict inclusion criteria
- 55 ml of whole blood was processed to produce 5 ml of PRP with a mean increase of 5.4x above baseline
- 2-3 ml of either PRP or bupivacaine (control) were injected using a 22-g needle into the common extensor tendon

Chronic Elbow Tendinosis


Results: Outcome Data

<table>
<thead>
<tr>
<th>Time</th>
<th>Visual Analog Pain Scores</th>
<th>Mean Mayo Elbow Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRP</td>
<td>Control</td>
</tr>
<tr>
<td>Initial</td>
<td>80.3</td>
<td>86</td>
</tr>
<tr>
<td>1 month</td>
<td>43.4</td>
<td>71.0</td>
</tr>
<tr>
<td>2 month</td>
<td>32.0</td>
<td>72</td>
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<tr>
<td>6 month</td>
<td>15.1</td>
<td>-</td>
</tr>
<tr>
<td>24 month</td>
<td>5.7</td>
<td>-</td>
</tr>
</tbody>
</table>

At 6 months, the PRP-treated patient's
1. Visual analog pain scores improved 81% (p<0.0001) over baseline
2. Mean mayo elbow scores improved 72% (p<0.0001) over baseline

Chronic Elbow Tendinosis

Key Points:
- PRP treated patients demonstrated significant improvement with a single injection that was sustained over time
- There were no reported complications (specifically, no infections, neurovascular changes, or worsening of patient's epicondylar pain)
- Treatment of patients with chronic elbow tendinosis with buffered PRP significantly reduced pain
- PRP may be considered before surgical intervention


PRP vs Corticosteroid in Lateral Epicondylitis: Netherlands Study. AJSM Feb 2010

- Purpose: determine effectiveness of PRP vs corticosteroid injection in patients with chronic LE
- Design: randomized controlled trial
- 100 patients
  - 51 PRP
  - 49 steroid
- Technique: peppering technique plus site of maximal tenderness
- Outcomes: VAS and DASH
- Successful treatment: >25% improvement in VAS or DASH without reintervention after 1 year

Peerbooms et al. AJSM. 2010. 38 (2)

PRP vs Corticosteroid in Lateral Epicondylitis: Netherlands Study. AJSM Feb 2010

- Results:
  - VAS scores: 49% improved in steroid group
  - VAS scores: 73% in the PRP group improved
  - DASH: 51% in steroid group improved
  - DASH: 73% in the PRP group
  - PRP group kept getting better over the next year.
  - PRP patients: 64% improvement in pain, 84% disability
  - Steroid group: 24% improvement in pain, 17% disability
Comparison of Surgically Repaired Achilles Tendon using Platelet-Rich Fibrin Matrices

- 12 male athletes with spontaneous complete rupture of Achilles tendon.
- 6 received platelet-rich fibrin matrices
- Regained ROM earlier (P= .025)
- Less time to take up gentle running (P= .042)
- Resumed training activities earlier (P= .004)
- Less increase in cross-sectional area (P= .009)


How can one platelet injection after tendon injury lead to a stronger tendon after 4 weeks?
Interplay between early regeneration and mechanical stimulation

Olga Vichenko and Per Aspengren

They studied the effects of platelets on Achilles tendon regenerates in rats 3, 5 and 14 days after transection. The tendons were either unloaded by Botulinum toxin A (Botox) injections into the calf muscles, or mechanically stimulated in activity cages. No Botox injections and ordinary cages, respectively, served as controls. Repair was evaluated by tensile testing.

Results At 14 days, unloading (with Botox) abolished any effect of the platelets and reduced the mechanical properties of the repair tissue to less than half of normal. Thus, some mechanical stimulation is a prerequisite for the effect of platelets at 14 days. Without Botox, both activity and platelets increased repair independently of each other. However, at 3 and 5 days, platelets improved the mechanical properties in Botox-treated rats.

Interpretation Platelets influence only the early phases of regeneration, but this allows mechanical stimulation to start driving neo-tendon development at an earlier time point, which kept it constantly ahead of the controls.
PRP and Tendon

- Gamradt et al 2007
  - Review of PRP application to enhance the healing of the repaired rotator cuff. They utilized a platelet rich fibrin matrix with sufficient density to maintain a suture for bone-interface.
  - Preliminary data demonstrated active growth factor release for at least 7 days.
  - Randomized clinical trial is underway.


- Blinded, prospective, randomized trial of PRP vs placebo in patients undergoing surgery to repair a torn rotator cuff.
- There was no difference in pain relief or in function between the 2, said Stephen C. Weber, MD.
- All patients had arthroscopic rotator cuff repair under general anesthesia, and those randomized to PRP received it at the conclusion of the repair.
- However, VAS scores and postoperative narcotic use did not differ between the 2 groups and, at 3 months postop, both groups showed residual defects on magnetic resonance imaging (MRI).

Medscape orthopedics 2010
Preliminary Response to JAMA article

This important study raises many important questions:

• A small sample size (# of enrollees). Studies of this size are generally regarded as preliminary

• Pre-injection with 2cc of marcaine (local anesthetic) is not commonly performed. That is a large volume relative to the size of the tendon and PRP injectate. Is there dilution or migration of PRP?

• These investigators buffered the PRP with 8.4% sodium bicarbonate. This changes the pH. The effects of PRP are believed to be pH dependent. This is an area of active research.

Review continued: JAMA article

• We have no parameters (measures) of degree of abnormality of the tendinopathy.

• Our protocols are different. We confirm at the time of injection that the patient is pain free to be confident the correct location was injected.

• They reported that 56-63% of patients experienced good to excellent results. Our average is 88% with good to excellent results with PRP treatment (in a broader array of diagnoses).

• Lastly, they did show a notable trend with 78% of the PRP group returning to desired sport vs. 67% of placebo group.

Monto et al. PRP in chronic achilles tendinopathy

• AAOS annual meeting March 19, 2010
• 30 patients with chronic refractory achilles tendinopathy > 8mos.
• 1 MSK US guided 4cc injection into abnormal area
• 48 hrs in CAM walker, then activity as tolerated
• AOFAS hindfoot scores improved
  • 34 pre
  • 84 post
  • 92 at 6 mos follow up
Digital tendon: Bosch et al 2009

- Ultrasonographic tissue characterization with computerized mathematical analysis and quantified regeneration during phases of repair after treatment of
  - Equine digital superficial flexor tendons with PRP or placebo
- Results:
  - Better healing properties in the PRP group
  - 80% of pixels demonstrated correct alignment in the PRP group compared with ~60% in the control group.

PRP and tendon

- Platelet-rich plasma: New clinical application A pilot study for treatment of jumper’s knee

Elizaveta Kon, Giuseppe Filardo et al. Injury 2009

- 20 male athletes with a mean history of 20.7 months of pain received treatment,
  - Baseline injection then 2 additional injections at 15 day intervals
  - PRP activated with Calcium chloride
- Outcomes were prospectively evaluated at 6 months follow-up.
- No severe adverse events were observed,
- Statistically significant improvements in all scores were recorded.
Fig. 4. Health status evaluated with EQ-VAS (means and CIs). CI, confidence interval; FU, follow-up.

Fig. 5. Sport activity level evaluated with the Tegner score (means and CIs). CI, confidence interval; FU, follow-up.

Fig. 6. Percentage of participants resuming sports after treatment, at different follow-up points.

- **Gaweda K et al.** Treatment of Achilles Tendinopathy with Platelet-Rich Plasma
  - 14 patients (15 tendons)
  - 3 cc PRP injected, no mention of platelet concentration
  - US guidance used
  - No mention of buffer
  - No mention of activator
  - No mention of lidocaine/marcaine
  - Rehab: PWB x 3 days, PROM x 2 wks, then active ROM, stretching from 2-6 wks, then >6 wks, full load active exercises (with heel lift)
  - No mention of eccentrics, no mention of RTP
  - Used US imaging to document healing of tendon (only study)

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- Significant improvement was observed in the clinical and imaging results.
- The AOFAS scale improved from a baseline median of 55 points to 98 points at 18 months (*p* = 0.000655), while the VISA-A scale improved from a baseline of 24 to 96 (*p* = 0.000655) in the final evaluations.
- During the final evaluation, one subject experienced minor pain following prolonged daily activity, while another subject complained of pain following overloading activity.
- **CONCLUSION:** Local, accurate PRP administration improved symptoms of non-insertional Achilles tendinopathy.

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PRP fails to improve long term outcome after surgical rotator cuff repair

- Randelli et al: *JSES, 2010.* PRP in arthroscopic rotator cuff repair: A prospective RCT study: 2 years follow up

  - Looked at double row repair in small to medium RTC tears
27 skeletally immature pigs underwent ACL transection and suture repair
Collagen-platelet composite (CPC) used to supplement the repair in 14 knees
Knees harvested at 4, 6, and 12 weeks. Mechanical testing and histologic analysis performed

Results: The addition of a CPC to a suture repair enhanced the structural properties of the ACL, and the improvement was associated with increased cellularity within the healing ligament.

Human ACL fibroblasts from immature patients have a stronger in vitro response to platelet concentrates than those from mature individuals
Human fibroblasts were obtained from 10 immature and adolescent patients
Wound healing cell migration, cell proliferation were higher in immature cells
No differences seen in wound contraction
Injection of PRP in Patients with Primary and Secondary Knee Osteoarthritis

- Sampson et al. AJPMR. Dec. 2010. PILOT study
  - Single center, uncontrolled, prospective preliminary study.
  - Three PRP injections in the affected knee at ~4 week intervals
  - Outcome measures: VAS, activities, expectation score and the Knee injury and osteoarthritis outcome scores.
  - 52 week follow up.
  - MSK ultrasound used to measure cartilage thickness

Sampson et al. 2010

- Results
  - Significant and almost linear improvements in Knee Injury and OA Outcome scores including pain and symptom relief
  - VAS improvements noted with movement and rest
  - Cartilage assessment limited by small sample
PRP and Joints


- Study: 71 patient (81 knees) retrospective cohort TKA study – The use of PRP lead to shortened hospital stay, improved ROM, improved hemoglobin profile, and a more stable hemodynamic profile.

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PRP and Joints


- Study: 98 patient retrospective cohort TKA study – The use of PRP lead to earlier functional ROM, shorter LOS, decreased IV and oral narcotic requirements, and lower hemoglobin drop in TKA patients.

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PRP and Joints

- Anitua E et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology. 2007;46(12):1769-72

- Increased hyaluronic acid secretion from knees of 10 arthritic patients using PRP
PRP and osteoarthritis

- Sanchez, Anitua et al. 2008. Clinical trial to evaluate intra-articular PRP vs hyaluron for knee OA
- Observational, retrospective cohort study.
- Administered 3 weekly intra-articular injections of PRP vs hyaluronan
- At week 5, 33% of PRP group improved vs 10% of hyaluronan group

PRP and Osteoarthritis

  - Notable improvement in functional and pain scores which remained positive at 6 mos.
  - Mild degradation of the scores at 1 year
  - Better outcome in lower grades of arthritis and younger patients

PRP and Knee Arthritis

- Kon et al from Rizzoli Orthopedic institute in Italy
- 150 patients randomized to PRP vs Hyaluronic acid injections
- PRP patients had better outcome at 6 mos.
- Best outcome: patients < 50yo

AAOS annual meeting  March 19, 2010
I was heading toward total knee replacement... Walking was minimal and difficult necessitating a cane or crutches... (fall 2008)

... I just returned from a trip to Bhutan where I made several day long hikes including one hike up and down a very steep incline to visit the famous “Tiger’s Nest” Monastery. (fall 2010)

I think the PRP therapy was able to turn things around so that I could increase my physical activity and strengthen my knee to the point where my activities include regular hiking...
Becker et al. Spine 2007

- 32 patients treated with epidural perineural injections with ACS
- 27 patients were treated with 5 mg triamcinolone
- 25 patients with 10 mg triamcinolone.
- Treatment was applied once per week for 3 consecutive weeks and followed for 6 months.
- The Visual Analogue Scale (VAS) of low back pain was the primary outcome measure.
- The Oswestry Disability Index (ODI)

Results:

- ACS or the 2 triamcinolone concentrations showed a clinically remarkable and statistically significant reduction in pain and disability.
- From Week 12 to the final evaluation at Week 22, injections with ACS showed a consistent pattern of superiority over both triamcinolone groups with regard to the VAS score for pain.
- Statistical significance was observed only at Week 22 in direct comparison to the triamcinolone 5 group. However, there was no statistically significant difference between the 2 triamcinolone dosages during the 6 months of the study.

Conclusion: ACS is an encouraging treatment option for patients with unilateral lumbar radicular compression. The decrease in pain was pronounced, clinically remarkable, and potentially superior to steroid injection.

PRP and Nerve

- Effect of Platelet-Rich Plasma on Peripheral Nerve Regeneration
- Yakup Sariguney et al. J of reconstr Microsurg 2008

This study evaluated the effect of platelet-rich plasma (PRP) in end-to-end neurorrhaphy in an experimental rat model of sciatic nerve injury.
**Sariguney et al. J of reconstr Microsurg 2008**

- The application of PRP to the repair site helped to improve remyelination of the sciatic nerve in rats when the epineural repair was done with six sutures.

**IOC consensus paper on the use of platelet rich plasma in sports medicine**


- **Suggested techniques and Post injection recommendations: consensus opinion**
  - Clinical examination
  - Ultrasound guidance recommended to verify accurate needle placement
  - No consensus on inside the tendon or around the tendon delivery
  - If PRP delivered during arthroscopy: suggest delivery after emptying the joint of arthroscopic fluid

**Suggested techniques and Post injection recommendations: IOC**

- In open surgery: use of one of the gels and semisolid forms
- In ALL cases, perform under strict asepsis
- Controversy re: use of concomitant NSAIDs or local anesthesia
- No general agreement on postinjection treatment
  - Rest, ice, limb elevation for 48hrs ?
  - Allow exercise after 2-5 days
  - Accelerated rehabilitation under appropriate supervision
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Limitations of Current Research

- Limited case series
- Small sample sizes
- No definition of standardized preparation of PRP
- Paucity of randomized controlled trials

Human Science Issues that require further study..... part 1

- Differential Effect of PRP on acutely injured tendon versus degenerative tendon
- Further human data on treatment of acute muscle injury. Timing? Hematoma aspiration?
- We need human data on treatment of chronic muscle injury (similar to tendinopathy)
- We need human data on treatment of osteoarthritis
- **Is there a separate mechanism for pain modulation distinct from the tissue healing?**
Basic science issues that require further study part 2

- In the treatment of acutely injured soft tissue (tendon, ligament, or muscle) the best time to inject PRP must be determined
- Is there a potential to exacerbate inflammation in acute injury
- Effect of serial injections should be explored
- Effects of local tissue pH and scaffold
- Necessity for percutaneous needle tenotomy
- Necessity for precision of musculoskeletal ultrasound guidance
- What are the optimal post-procedure protocols?

Research Collaboration

- Emory
- NJ Medical School
- Harvard
- Mayo
- U Wash Seattle

THE BUZZ IS IN THE AIR...

Ljungqvist et al., Jan 2008
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- As it relates to musculoskeletal and sports medicine, this includes
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  - Extracorporeal shock wave therapy
  - Platelet rich plasma
  - Nitric oxide
  - Matrix metalloproteinase
  - Mesenchymal stem cells

"Wow, that's the worst case of tennis elbow I've seen this year!"
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- Contains growth factors secreted by alpha granules of platelets
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  - TGFβ1 and TGFβ2
  - Vascular endothelial growth factor
  - Epithelial growth factor

Alpha Granules
- Platelet derived growth factor (PDGF)
- Transforming growth factor (TGF)
- Epidermal growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor (FGF)
- Connective tissue growth factor (CTGF)

Dense Granules
- Serotonin
- ADP
- Histamine
- Calcium

TREATMENT: PRP INJECTION

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PRP Human Studies

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- Tendon
- Ligament
- Muscle
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- Arthritis
- Nerve

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Chen-Ching Chiang, MD; Chou-Tai Su, DDS, FRC; Ching-Kai Tsuang, MD; Wei-Ming Chen, MD; Tai-Wen Chang, MD; and Yu-Huan Tsang, MD

Background: Bone-marrow stem cells were harvested from the iliac crest of each patient, and the growth medium was processed using a centrifugation technique. They were reintroduced with autologous bone marrow and a platelet-rich plasma (PRP) gel.

Methods: Ten patients with three tibial and eight femoral nonunions after multiple prior procedures were included. All patients were treated with the bone-grafting procedure, with and without PRP. Ten patients with other external fixators were treated with PRP, and the time to union was determined.

Results: The 10 patients treated with PRP had a mean time to union of 18.7 weeks after the first attempt and 11.3 weeks after the second attempt. The bone mineral density increased steadily from early healing to the remodeling phase.
PRP and Bone

- Plachokova et al.
- Systematic review of PRP on bone regeneration in dentistry
- "Found evidence for beneficial effects of PRP in the treatment of periodontal defects"


PRP: osteoinductive effect


- Sheep infraspinatus repair model using MRI scan and histology.
- Study demonstrated an increased formation of new bone and fibrocartilage at the healing site.

PRP and Muscle
PRP and Muscle

- Sanchez M, et al; “Application of Autologous Growth Factors on Skeletal Muscle Healing”, *World Congress on Regenerative Medicine Podium Presentation, May 18, 2005*

- Study: 20 patient prospective acute muscle injury pilot study with 6 month follow-up – Ultrasound guided injection of PRP.
  - Multiple, serial prp injections at one week intervals to defect sites after hematoma evacuation
  - Ultrasound demonstrated injured muscle healed fully without fibrosis. Functional capacities 50% faster than the control group.
  - The athletes had full recovery in half the expected times

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PRP and Muscle

  - Pilot study
  - Professional athletes with muscle strain
  - Administered autologous conditioned serum
  - Control group received actovegin/traumeel
  - Found a reduction in recovery time in return to 100% activity in competitive sports. (16 days vs 22 days in the control group)
  - MRI recovery time was accelerated as well.

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PRP and Muscle

  - Tib anterior of rats injected with PRP or PPP for treatment of acute muscle strain (high repetition multiple small strains vs single large strain)
  - Conclusion: "local delivery of PRP can shorten recovery time after a muscle strain injury in a small animal model."
  - Recovery of muscle from a high repetition model has been shown to require myogenesis. This may explain why PRP was more effective in the high-repetition protocol.
PRP and muscle

- Cugat: unpublished case series 2005
  - International society of arthroscopy
  - 14 professional athletes
  - 16 muscular injuries (soccer and basketball)
  - PRP injected under ultrasound after hematoma aspiration
  - 50% reduction in time to return to play in less severe injuries.
  - RTP diminished in each group according to severity

PRP and Tendon

Aim: IRB approved prospective pilot study to evaluate the efficacy of using PRP as a potential treatment for chronic severe epicondylar tendinosis.

Methods: 140 patients were evaluated for this study
  - 20 patients (15%) met strict inclusion criteria
  - 55 ml of whole blood was processed to produce 5 ml of PRP with a mean increase of 5.4x above baseline
  - 2-3 ml of either PRP or bupivacaine (control) were injected using a 22-g needle into the common extensor tendon

### Chronic Elbow Tendinosis

**Results:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Visual Analog Pain Scores</th>
<th>Mean Mayo Elbow Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRP</td>
<td>Control</td>
</tr>
<tr>
<td>Initial</td>
<td>80.3</td>
<td>68</td>
</tr>
<tr>
<td>1 month</td>
<td>43.4</td>
<td>71.0</td>
</tr>
<tr>
<td>2 month</td>
<td>32.0</td>
<td>72</td>
</tr>
<tr>
<td>6 month</td>
<td>15.1</td>
<td>-</td>
</tr>
<tr>
<td>24 month</td>
<td>5.7</td>
<td>-</td>
</tr>
</tbody>
</table>

At 6 months, the PRP-treated patient:

1. Visual analog pain score improved 81% (p<0.0001) over baseline
2. Mean mayo elbow score improved 72% (p<0.0001) over baseline

**Key Points:** PRP treated patients demonstrated significant improvement with a single injection that was sustained over time.

There were no reported complications (specifically, no infections, neurovascular changes, or worsening of patient's epicondylar pain).

Treatment of patients with chronic elbow tendinosis with buffered PRP significantly reduced pain.

PRP may be considered before surgical intervention.

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### PRP vs Corticosteroid in Lateral Epicondylitis: Netherlands Study. AJSM Feb 2010

- **Purpose:** determine effectiveness of PRP vs corticosteroid injection in patients with chronic LE
- **Design:** randomized controlled trial
  - 100 patients
    - 51 PRP
    - 49 steroid
- **Technique:** peppering technique plus site of maximal tenderness
- **Outcomes:** VAS and DASH
- **Successful treatment:** >25% improvement in VAS or DASH without reintervention after 1 year
PRP vs Corticosteroid in Lateral Epicondylitis: Netherlands Study. AJSM Feb 2010

• Results:
  • VAS scores: 49% improved in steroid group
  • VAS scores: 73% in the PRP group improved
  • DASH: 51% in steroid group improved
  • DASH: 73% in the PRP group
  • PRP group kept getting better over the next year.
    • PRP patients: 64% improvement in pain, 84% disability
    • Steroid group: 24% improvement in pain, 17% disability

Comparison of Surgically Repaired Achilles Tendon using Platelet-Rich Fibrin Matrices

• 12 male athletes with spontaneous complete rupture of Achilles tendon.
  • 6 received platelet-rich fibrin matrices
  • Regained ROM earlier (P= .025)
  • Less time to take up gentle running (P=.042)
  • Resumed training activities earlier (P=.004)
  • Less increase in cross-sectional area (P=.009)


How can one platelet injection after tendon injury lead to a stronger tendon after 4 weeks? Interplay between early regeneration and mechanical stimulation

Olga Vinchenko and Per Aspdenberg

• They studied the effects of platelets on Achilles tendon regenerates in rats 3, 5 and 14 days after transection. The tendons were either unloaded by Botulinum toxin A (Botox) injections into the calf muscles, or mechanically stimulated in activity cages. No Botox injections and ordinary cages, respectively, served as controls. Repair was evaluated by tensile testing.
Results At 14 days, unloading (with Botox) abolished any effect of the platelets and reduced the mechanical properties of the repair tissue to less than half of normal. Thus, some mechanical stimulation is a prerequisite for the effect of platelets at 14 days. Without Botox, both activity and platelets increased repair independently of each other. However, at 3 and 5 days, platelets improved the mechanical properties in Botox-treated rats.

Interpretation Platelets influence only the early phases of regeneration, but this allows mechanical stimulation to start driving neo-tendon development at an earlier time point, which kept it constantly ahead of the controls.

PRP and Tendon

- Gamradt et al 2007
  - Review of PRP application to enhance the healing of the repaired rotator cuff. They utilized a platelet rich fibrin matrix with sufficient density to maintain a suture for bone-interface
  - Preliminary data demonstrated active growth factor release for at least 7 days.
  - Randomized clinical trial is underway.


- Blinded, prospective, randomized trial of PRP vs placebo in patients undergoing surgery to repair a torn rotator cuff,
- There was no difference in pain relief or in function between the 2, said Stephen C. Weber, MD,
- All patients had arthroscopic rotator cuff repair under general anesthesia, and those randomized to PRP received it at the conclusion of the repair.
- However, VAS scores and postoperative narcotic use did not differ between the 2 groups and, at 3 months postop, both groups showed residual defects on magnetic resonance imaging (MRI).

Medscape orthopedics 2010
Preliminary Response to JAMA article

This important study raises many important questions:

• A small sample size (# of enrollees). Studies of this size are generally regarded as preliminary.

• Pre-injection with 2cc of marcaine (local anesthetic) is not commonly performed. That is a large volume relative to the size of the tendon and PRP injectate. Is there dilution or migration of PRP?

• These investigators buffered the PRP with 8.4% sodium bicarbonate. This changes the pH. The effects of PRP are believed to be pH dependent. This is an area of active research.

Review continued: JAMA article

• We have no parameters (measures) of degree of abnormality of the tendinopathy.

• Our protocols are different. We confirm at the time of injection that the patient is pain free to be confident the correct location was injected.

• They reported that 56-63% of patients experienced good to excellent results. Our average is 88% with good to excellent results with PRP treatment (in a broader array of diagnoses).

• Lastly, they did show a notable trend with 78% of the PRP group returning to desired sport vs. 67% of placebo group.
Monto et al. PRP in chronic achilles tendinopathy

- AAOS annual meeting March 19, 2010
- 30 patients with chronic refractory achilles tendinopathy > 8mos.
- 1 MSK US guided 4cc injection into abnormal area
- 48 hrs in CAM walker, then activity as tolerated
- AQFAS hindfoot scores improved
  - 34 pre
  - 84 post
  - 92 at 6 mos follow up

Digital tendon: Bosch et al 2009

- Ultrasonographic tissue characterization with computerized mathematical analysis and quantified regeneration during phases of repair after treatment of
  - Equine digital superficial flexor tendons with PRP or placebo
- Results:
  - Better healing properties in the PRP group
  - 80% of pixels demonstrated correct alignment in the PRP group compared with ~60% in the control group.

PRP and tendon

- Platelet-rich plasma: New clinical application A pilot study for treatment of jumper's knee

Elizaveta Kon, Giuseppe Filardo et al. Injury 2009
- 20 male athletes with a mean history of 20.7 months of pain received treatment.
- Baseline injection then 2 additional injections at 15 day intervals
- PRP activated with Calcium chloride
- Outcomes were prospectively evaluated at 6 months follow-up.
- No severe adverse events were observed.
- Statistically significant improvements in all scores were recorded.

Fig. 4. Health status evaluated with EQ-VAS (means and CIs). CI, confidence interval; FU, follow-up.

Fig. 5. Sport activity level evaluated with the Tegner score (means and CIs). CI, confidence interval; FU, follow-up.

- **Gaweda K et al.**, Treatment of Achilles Tendinopathy with Platelet-Rich Plasma
  - 14 patients (15 tendons)
  - 3 cc PRP injected, No mention of platelet concentration
  - US guidance used
  - No mention of buffer
  - No mention of activator
  - No mention of lidocaine/marcaine
  - Rehab: PWB x 3 days, PROM x 2 wks, then active ROM, stretching from 2-6 wks, then >6 wks, full load active exercises (with heel lift)
  - No mention of eccentrics, no mention of RTP
  - Used US imaging to document healing of tendon (only study)

- **CONCLUSION**: Local, accurate PRP administration improved symptoms of non-insertional Achilles tendinopathy.

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Significant improvement was observed in the clinical and imaging results.

- The AOFAS scale improved from a baseline median of 55 points to 96 points at 18 months (p=0.000655), while the VISA-A scale improved from a baseline of 24 to 96 (p=0.000655) in the final evaluations.

- During the final evaluation, one subject experienced minor pain following prolonged daily activity, while another subject complained of pain following overloading activity.

- **CONCLUSION**: Local, accurate PRP administration improved symptoms of non-insertional Achilles tendinopathy.
PRP fails to improve long term outcome after surgical rotator cuff repair

- Randelli et al: *JSES, 2010*. PRP in arthroscopic rotator cuff repair: A prospective RCT study: 2 years follow up


- Looked at double row repair in small to medium RTC tears

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PRP and Ligament

- 27 skeletally immature pigs underwent ACL transection and suture repair
- Collagen-platelet composite (CPC) used to supplement the repair in 14 knees
- Knees harvested at 4, 6, and 12 weeks. Mechanical testing and histologic analysis performed

- **Results**: The addition of a CPC to a suture repair enhanced the structural properties of the ACL, and the improvement was associated with increased cellularity within the healing ligament

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- **Magarian et al.** *Knee.* 2010 Aug 19
  - Human ACL fibroblasts from immature patients have a stronger in vitro response to platelet concentrates than those from mature individuals.
  - Human fibroblasts were obtained from 10 immature and adolescent patients.
  - Wound healing cell migration, cell proliferation were higher in immature cells.
  - No differences seen in wound contraction.

**PRP and Joints/Cartilage**

**Injection of PRP in Patients with Primary and Secondary Knee Osteoarthritis**
- **Sampson et al.** *AJPMR.* Dec. 2010. PILOT study.
  - Single center, uncontrolled, prospective preliminary study.
  - Three PRP injections in the affected knee at ~4 week intervals.
  - Outcome measures: VAS, activities, expectation score and the Knee injury and osteoarthritis outcome scores. 52 week follow up.
  - MSK ultrasound used to measure cartilage thickness.
Results

- Significant and almost linear improvements in Knee Injury and OA Outcome scores including pain and symptom relief
- VAS improvements noted with movement and rest
- Cartilage assessment limited by small sample

PRP and Joints


- Study: 71 patient (81 knees) retrospective cohort TKA study – The use of PRP lead to shortened hospital stay, improved ROM, improved hemoglobin profile, and a more stable hemodynamic profile.

PRP and Joints


- Study: 98 patient retrospective cohort TKA study – The use of PRP lead to earlier functional ROM, shorter LOS, decreased IV and oral narcotic requirements, and lower hemoglobin drop in TKA patients.
PRP and Joints

- Anitua E et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology. 2007;46(12):1769-72
- Increased hyaluronic acid secretion from knees of 10 arthritic patients using PRP

PRP and osteoarthritis

- Sanchez, Anitua et al 2008. Clinical trial to evaluate intra-articular PRP vs hyaluron for knee OA
  - Observational, retrospective cohort study.
  - Administered 3 weekly intra-articular injections of PRP vs hyaluronan
  - At week 5, 33% of PRP group improved vs 10% of hyaluronan group

PRP and Osteoarthritis

  - Notable improvement in functional and pain scores which remained positive at 6 mos.
  - Mild degradation of the scores at 1 year
  - Better outcome in lower grades of arthritis and younger patients
PRP and Knee Arthritis

- Kon et al from Rizzoli Orthopedic institute in Italy
- 150 patients randomized to PRP vs Hyaluronic acid injections
- PRP patients had better outcome at 6 mos.
- Best outcome: patients < 50yo

AAOS annual meeting March 19, 2010

- I was heading toward total knee replacement....Walking was minimal and difficult necessitating a cane or crutches. ..... (fall 2008)
- ..... I just returned from a trip to Bhutan where I made several day long hikes including one hike up and down a very steep incline to visit the famous "Tiger's Nest" Monastery.  (fall 2010)
- I think the PRP therapy was able to turn things around so that I could increase my physical activity and strengthen my knee to the point where my activities include regular hiking. .....
PRP and Nerve

- Efficacy of Epidural Perineural Injections With Autologous Conditioned Serum for Lumbar Radicular Compression: An Investigator-Initiated, Prospective, Double-Blind, Reference-Controlled Study

Cordelia Becker, MD et al. Spine 2007

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Becker et al. Spine 2007

- 32 patients treated with epidural perineural injections with ACS
- 27 patients were treated with 5 mg triamcinolone
- 25 patients with 10 mg triamcinolone.
- Treatment was applied once per week for 3 consecutive weeks and followed for 6 months.
- The Visual Analogue Scale (VAS) of low back pain was the primary outcome measure.
- The Oswestry Disability Index (ODI)

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Results:

- ACS or the 2 triamcinolone concentrations showed a clinically remarkable and statistically significant reduction in pain and disability.
- From Week 12 to the final evaluation at Week 22, injections with ACS showed a consistent pattern of superiority over both triamcinolone groups with regard to the VAS score for pain.
- Statistical significance was observed only at Week 22 in direct comparison to the triamcinolone 5 group. However, there was no statistically significant difference between the 2 triamcinolone dosages during the 6 months of the study.
- Conclusion: ACS is an encouraging treatment option for patients with unilateral lumbar radicular compression. The decrease in pain was pronounced, clinically remarkable, and potentially superior to steroid injection.
PRP and Nerve

- Effect of Platelet-Rich Plasma on Peripheral Nerve Regeneration
  - **Yakup Sariguney et al. J of reconstr Microsurg 2008**

  - This study evaluated the effect of platelet-rich plasma (PRP) in end-to-end neurorrhaphy in an experimental rat model of sciatic nerve injury.

Sariguney et al. J of reconstr Microsurg 2008

- The application of PRP to the repair site helped to improve remyelinization of the sciatic nerve in rats when the epineural repair was done with six sutures.

IOC consensus paper on the use of platelet rich plasma in sports medicine

  - **Br J Sports Med 2010;44:1072-1081**

  - **Suggested techniques and Post injection recommendations:** consensus opinion
    - Clinical examination
    - Ultrasound guidance recommended to verify accurate needle placement
    - No consensus on inside the tendon or around the tendon delivery
    - If PRP delivered during arthroscopy: suggest delivery after emptying the joint of arthroscopic fluid
Suggested techniques and Post injection recommendations: IOC

- In open surgery: use of one of the gels and semisolid forms
- In ALL cases, perform under strict asepsis
- Controversy re: use of concomitant NSAIDs or local anesthesia
- No general agreement on postinjection treatment
  - Rest, ice, limb elevation for 48hrs?
  - Allow exercise after 2-5 days
  - Accelerated rehabilitation under appropriate supervision

Summary
Conclusions
Future Research

Limitations of Current Research

- Limited case series
- Small sample sizes
- No definition of standardized preparation of PRP
- Paucity of randomized controlled trials
Human Science Issues that require further study..... part 1

- Differential Effect of PRP on acutely injured tendon versus degenerative tendon
- Further human data on treatment of acute muscle injury. Timing? Hematoma aspiration?
- We need human data on treatment of chronic muscle injury (similar to tendinopathy)
- We need human data on treatment of osteoarthritis
- **Is there a separate mechanism for pain modulation distinct from the tissue healing?**

Basic science issues that require further study part 2

- In the treatment of acutely injured soft tissue (tendon, ligament, or muscle) the best time to inject PRP must be determined
- Is there a potential to exacerbate inflammation in acute injury
- Effect of serial injections should be explored
- Effects of local tissue pH and scaffold
- Necessity for percutaneous needle tenotomy
- Necessity for precision of musculoskeletal ultrasound guidance
- What are the optimal post-procedure protocols?

Research Collaboration

- Emory
- NJ Medical School
- Harvard
- Mayo
- U Wash Seattle