Platelet-Rich Plasma in the Lower Extremity

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Objectives

- To discuss the history and definition of platelet-rich plasma as it pertains to orthopedic sports medicine
- Define PRP
- How it works?
- Indications
- Applications
Introduction

• In Orthopedics we continue the quest to find ways to enhance healing.
• Accelerated healing means quicker return to play

Introduction

• PRP is defined as autologous blood with a concentration of platelets above baseline values
  Normal:
  - 150,000 and 450,000 platelets per microliter (mcL)
  - Males average: 237,000 per mcL
  - Females average: 266,000 per mcL
• In vitro studies suggest that growth factors released by platelets recruit reparative cells and may augment soft tissue repair.

Various Options Available

• There are numerous investigational options available which can enhance and accelerate healing:
  – Amniofix (Primitive cells)
  – ACP (Autologous Conditioned Plasma w/ 2-3x platelets)
  – Stem Cells (Similar to PRP from bone marrow aspirate)
  – Orthokine Therapy (only available in Europe)
    • Kobe Bryant, Alex Rodriguez
  – PRP (Platelet Rich plasma w/ 4-8x platelets)
Available Systems for PRP/ACP

Introduction

- PRP has been utilized in orthopedic surgery for >20 years
- Recent interest in use of PRP in Sports injuries
- Theoretically influence healing of tendon, ligament and muscle

Introduction

- PRP contains growth factors which work in all three phases of connective tissue healing:
  - Inflammation
  - Proliferation
  - Remodeling
- Tendon
  - Increased cell proliferation and total collagen production by tenocytes
  - Increased type I and type III collagen
- Muscle
  - Increased myogenensis and regulate the level of fibrosis
Why PRP?

History of PRP

- Utilized and studied since the 1970s
- Used primarily in maxillofacial and plastic surgery up until recently
- First used in orthopaedics for an adjunct to spinal fusion surgery as bone graft (questionable efficacy for fusions)
- Role in muscle and tendon healing has become popular in the last few years in orthopedics
- Numerous animal studies, basic science studies, and case reports/level IV studies in literature; few controlled trials

Basic Science

- Normal Plasma: 150,000-350,000 platelets/µL in 5 mL
- Definition of PRP: platelet rich >=1,000,000 platelets/µL in 5 mL of plasma
- Platelets:
  - proteins, cytokines, bioactive factors
  - initiate and regulate basic aspects of wound healing
- Plasma: fluid portion of blood that contains clotting factors and other proteins
Basic Science

- PRP: 3 to 5 fold increase in growth factor concentrations contained within α-granules
  - TGF-β, PDGF, IGF-I and II, FGF, VEGF, and endothelial cell growth factor
  - These cytokines play a role in cell proliferation, chemotaxis, cell differentiation and angiogenesis
  - These cytokines are present in normal biologic ratios in PRP vs. BMP
- PRP is not: “platelet gel”, “fibrin glue”, or “platelet concentrate”

Stages of Healing

- Other Bioactive factors in granules (non-growth factors)
  - serotonin, histamine, dopamine, calcium, and adenosine
- Fundamental effects on healing, particularly inflammation stage
- Platelets in PRP are delivered in a clot
  - contains several adhesion molecules that play a role in cell migration
  - clot itself acts as a scaffold
Major Indications for PRP

- Chronic (Tendinopathies)
  - Adjuvant to Non-Healing tissue
  - Introduce Growth Factors to increase rate of healing
  - Stimulate healing in chronic tendinopathy
- Acute (Ligamentous/muscle injuries)
  - Reduce return to play time
  - Accelerate ligament and muscle healing
- Intraoperative Augmentation

Preparing PRP

- Made from anti-coagulated blood; whole blood clots incorporate all the platelets
- First centrifuge: separates red blood cells from white blood cells, plasma, and platelets
- Second centrifuge: further concentrates platelets, producing the PRP separate from platelet-poor plasma

- PRP may/may not be clotted to allow for delivery
  - Degradation begins
  - 70% of stored growth factors are released within 10 minutes
  - 100% within 1 hour
  - Calcium chloride/thrombin to activate
- Lifespan of platelet is 8-10 days
Effects of PRP

Essentially, PRP is adding multiple numbers of the same growth factors/cytokines that are needed in each phase of healing...theoretically speeding up the process
- Specifically aimed at soft tissue: tendon, ligament, muscle and skin
- Effect on tendon: increased cell proliferation and total collagen production; rats are getting back into the maze faster
- Effect on muscle: basic FGF and IGF-I are known cytokines that improve muscle healing

Clinical Applications

- Historically, PRP used for chronic tendinopathies
- Newest literature uses PRP for acute ligamentous and muscle injuries to expedite return to play
- Indications for use have outpaced the basic science and clinical trials validating the efficacy

Clinical Applications

- Chronic tendinopathy
  - Epicondylitis
  - Achilles
  - Patellar tendon
  - Plantar fascia
  - Osteoarthritis
- Intra-operative (bone healing)
  - TKA
  - ACL reconstruction
  - Acute Achilles repair
  - Rotator cuff repair
  - Acute articular cartilage repair
- Acute Muscle Injuries (strains)
Contraindications

- Septicemia, Thrombocytopenia, or Anemia
- Pregnancy
- Platelet dysfunction syndrome
- Hypofibrinogenemia
- History of corticosteroid injection at the treatment site or systemic with in 2 wks
- NSAIDS with in 48 hours
- Recent fever or illness/active infection
- History of cancer/active tumor

Achilles tendinopathy

- Tendonitis vs Tendinopathy:
- Inflammation vs Microtears (mucinoid degeneration)
- PRP is not indicated for paratendinitis alone (if that exists)
- Refractory Achilles tendinopathy pts who have failed multiple PT rounds and other conservative modalities
- Protection with brace advocated after injection, as is cessation of athletic activity
- Gradual return to activities/sport in 10-12 weeks

Results

- Use in Achilles tendinopathy
- de Jonge et al., 2011, AJSM
- Double-blind randomized placebo-controlled study
- 27 in PRP group and 27 in control group
- No statistically significant difference pain score and activity level
Plantar fasciitis

- Chronic refractory plantar fasciitis pts who have failed PT and multiple conservative modalities such as orthoses, NSAIDs, and cortisone shots
- No data on whether PRP is beneficial for pts with tears of plantar fascia
- Immediate WB and PT protocol after injection
- Gradual return to activities over 6-8 weeks, longer for running athletes

Results

- Barrett and Erredge, 2004
- Retrospective, cohort
- 9 patients
- 7/9 with complete pain relief at one year

Patellar tendinopathy

- Demonstrated intra-substance changes on MRI or US; most commonly found at the proximal bone-tendon junction
- Severe symptoms present for more than three months
- Treatment of chronic patellar tendinopathy as an adjunct to rest and PT
- May be used as an alternative to surgical treatment after failed conservative therapy
- “Washout period” recommended for a week at least (no NSAIDs)
Results

- Kon et al., 2009
- Prospective, cohort
- 20 patients
- 70% with marked or complete improvement
- 80% satisfied

Acute Ligamentous Injury

- MCL sprains

Results

- Mandelbaum and Gerhardt, AJSM Nov 2009
- Retrospective
- 22 professional soccer players with Grade II MCL
- PRP in <72 hours from injury
- RTP shortened by 27% compared to control group
MCL injury

- MCL, see disruption of MCL fibers, not a complete tear
- Post PRP

Acute Muscle Injury

- Acute grade 2-3 muscle strains
- Acute severe muscle contusion
- Muscle healing follows same stages as wounds
- May decrease return to play times
- Concerns regarding potential fibrotic healing response

Results

- Sanchez et al., 2009
- Prospective, cohort
- 22 muscle injuries in 20 high level professional athletes
- Full recovery in half the time in all patients
Intra-operative Uses

- TKA: Earliest uses of PRP in Orthopedics were in pts who had undergone TKA
- Primary indication is to promote wound healing and decrease blood loss

Results

- Berghoff et al., 2006
  - 66 TKR pts in control group, 71 in intervention group
  - Autologous PRP fibrin sealant sprayed in knee prior to closure
  - Results:
    - higher postoperative hgb
    - shorter hospital stays
    - less incidence of transfusion
    - fewer narcotics taken
    - better knee ROM at 6 week follow-ups

Intraoperative use in ACL

- Various preparations and uses have been attempted
Results

- Orrego et al., 2008
  - Randomized controlled trial
  - 108 ACL reconstruction patients
  - PRP injected grafts versus non-PRP grafts
  - Enhanced graft maturation process evaluated by MRI
  - No difference in tunnel widening or bone-tendon interface

- Silva and Sampio, 2009
  - Prospective, cohort
  - No difference in MRI signal intensity at 3 mos

Intra-operative Uses

- Acute achilles tendon repair: augmenting primary repair in athletes

Results

- Sanchez et al (AJSM 2007)
  - Case-control
  - 12 patients with Achilles repair
  - compared this group with age-matched controls having primary repair and no PRP
  - Faster return of ROM, jumping and jogging than control group
Use in Osteoarthrosis

- Acute articular cartilage repair/treatment of degenerative joint disease

Results

- Bennett and Schultz (American Journal of Surgery, 1993)
  - first described good results using PRP for articular cartilage lesions; type II collagen synthesis and induction of chondrogenesis from mesenchymal stem cells were reported
- Wu et al (Med Hypotheses, 2009)
  - suggested that PRP can be used as a chondrocyte carrier for treatment of acute cartilage lesions of the knee (no data regarding outcomes as of yet)

Results

- Cugat, 2011
  - 312 with osteoarthritis
  - 3 intra articular injections
  - Quality of life questionnaires at 6 months
  - Improvements in function and quality of life by OA specific clinical assessment instruments
Regulation of PRP in Sports

WADA: World Anti-Doping Agency

- Official Stance:
  - PRP does not demonstrate potential for performance enhancement beyond a potential therapeutic effect
  - Restricted to use in tendons or musculotendinous junction
  - NOT APPROVED in the muscle itself

Regulation of PRP in Sports

- Truth? PRP is unlikely to provide an athletic advantage because unbound IGF-I has too short of a half-life (10 minutes to 16 hrs) to provide a performance advantage
- Also isoform IGF-Iea (found in PRP) is not the isoform responsible for muscle hypertrophy (IGF-Iec/MGF)
- Finally, the dose of IGF-I is sub-therapeutic (300 µg) to produce a systemic anabolic effect (160 mg)

Regulation of PRP in Sports

- Olympic-affiliated and international anti-doping governing bodies have no jurisdiction over professional sports leagues in the US (NBA, MLB, NFL, NHL)
- PRP is not specifically addressed in any of the lists of banned substances to date
- Throughout the literature, there is no suggestion that PRP has a systemic effect or provides a sports advantage; only anecdotal reports exist suggesting that PRP accelerates the repair of an (acutely) injured area
Potential Advantages

- Low chance of rejection (pts own blood)
- PRP can be prepared at the time of care in a simple and relatively inexpensive manner (vs stem cells)

Potential Limitations

- Optimal dose range of PRP has yet to be defined
- Theoretical cancer-like effect of uncontrolled differentiation of cells
- Review of literature shows a clear lack of standardization in the preparation of PRP
- Uniform protocols and quantification of standard platelet yields are necessary
- ACP (autologous conditioned plasma) vs. PRP: is it Arthrex or less WBC’s that make it better?
- Timing and number of treatments

Conclusion

- PRP and PRP-related products have been applied to a diversity of tissues in a variety of surgical fields
- Goal of PRP is to deliver a high concentration of platelet-growth factors to enhance healing response
- PRP may be advantageous in sports medicine, but little evidence other than case series and reports exist to support PRP’s effectiveness
- A significant amount of basic science and clinical research needs to be done to define PRP’s role
References


Thank You!