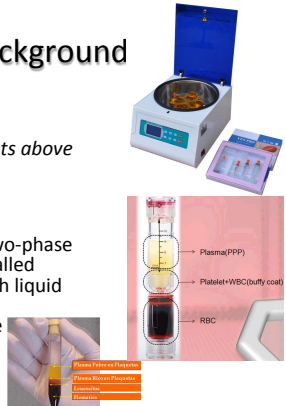



**Hospital del Mar**  
 Joan C. Manllau MD, PhD  
 Hot Topics in ACL  
 Place of PRP  
  
 5th Advanced course on knee surgery  
 February 2nd to 7th 2014. Val d'Isère. France

### PRP Background

- Defined as "a sample of autologous blood with concentrations of platelets above baseline values"
- It is created through a two-phase centrifugation process called plasma-pheresis, in which liquid and solid components of anticoagulated blood are separated



### PRP Background

- Proteins such as *platelet-derived growth factor* (PDGF), *vascular endothelial growth factor* (VEGF), *endothelial cell growth factor*, and *basic fibroblast growth factor* can be detected at high concentrations

→ PRP may be beneficial in conditions that require tissue healing

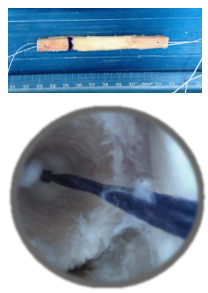
### PRP Background

- Other proteins present in PRP have demonstrated **inhibitory effects**, such as *Transforming Growth Factor (TGF)-β1*, which may lead to variable clinical results in certain applications.

→ Controversy

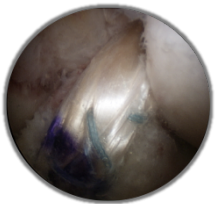
### ACL Reconstruction

- Current gold standard for treating ACL tears (autogeneic or allogeneic tendon grafts)
- Two main biologic processes
  - **ligamentization** of the tendon graft
  - **graft-to-bone healing** in the femoral and tibial tunnels



### Biology of ACL Reconstruction Ligamentization

- Graft maturation** → necessary for optimal biomechanical strength and return to activity
- Graft remodeling** may be accelerated by the actions of → PDGF, TGF-β1, and *insulin-like growth factor-1*



Radice et al. Comparison of magnetic resonance imaging findings in ACL grafts with and without autologous platelet-derived growth factors. Arthroscopy 2010

### Biology of ACL Reconstruction Tendon to Bone Healing

- **Tendon to Bone Healing** → takes a long time (12 weeks)  
Rodeo JBJS Am 1993
- **Growth Factors** (some) have been proven to augment or enhance the tendon-bone healing process *in vitro* →
  - Bone Morphogenetic Protein-2 (BMP-2)
  - Transforming Growth Factor (TGF)
  - Fibroblast growth factor (FGF)

Wahlstrom et al. Generation of tendon-to-bone interface "rafts" with use of recombinant BMP-2 in a rabbit model. J Orthop Res 2007  
Hosomi et al. The effect of transforming growth factor beta1 on continuous healing of human anterior cruciate ligament of ACL injury. Arthroscopy 2002  
Matsuda et al. Enhancement of tendon-bone integration of anterior cruciate ligament grafts with bone morphogenetic protein-2 gene transfer: A histological and biomechanical study. J Bone Joint Surg Am 2002

### ACL Reconstruction Rationale of using PRP

*In vitro* →

- Platelet rich plasma improves ACL cells viability and function

Day	10% PRP	20% PRP	30% PRP
Day 1	~0.3	~0.4	~0.5
Day 2	~0.4	~0.6	~0.8
Day 4	~0.6	~0.9	~1.1

Falouh et al. Effects of autologous platelet-rich plasma on cell viability and collagen synthesis in injured human anterior cruciate ligament. J Bone Joint Surg Am 2010

### ACL Reconstruction Rationale of using PRP

- **Early administration of PRP** (during the inflammatory process) may lead to an **accelerated healing cascade** (shorter than the typical period expected for full graft maturation and integration)

**The goals**  
to increase histologic metrics in repair and remodelling of the graft  
to improve tunnel healing  
to decrease donor site morbidity

Sánchez et al. Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: Gross morphology and histology. Arthroscopy 2010

### Clinical studies

Tendon-Bone healing  
Graft maturation  
Tendon-Bone healing

### PRP and ACL Reconstruction

- **Methods**
  - Prospective, single-blind study, 1y FU
  - 50 pts treated with either ACL autograft or ACL autograft + PRP gel at the time of surgery
- **Results**
  - significantly faster (177 vs 369 days) biologic maturation in the group of PRP (MRI)

**Graft maturation**

6 months FU

Radice et al. Comparison of magnetic resonance imaging findings in anterior cruciate ligament grafts with and without autologous platelet-derived growth factors. Arthroscopy 2010

### PRP and ACL Reconstruction

- **Methods**
  - RCT, 108 patients
  - Addition of platelet concentrate to a ST-gracilis graft and to the femoral tunnel
- **Results**
  - At 6 months FU
    - Higher rate ( $P = 0.036$ ) of graft maturation (low-intensity signal on MRI)
    - No significant effect in osteoligamentous interface

**Graft maturation**  
**Tunnel healing**

Orrego et al. Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel. Arthroscopy 2008

## PRP and ACL Reconstruction


Knee Function

**Methods**

- Fifty patients allograft ACL-R with intra-operative application of PRP to the graft matched with 50 allograft ACL-R without PRP use

**Results**

- Decreased effusions at 10 ± 4 days in the PRP group (this difference disappeared by 8 ± 4 weeks)
- No differences between groups
  - additional surgeries or complications in the first 2y after reconst.
- No differences in patient-reported outcomes (patients with two-year outcome data)



Magnussen et al. Platelet rich plasma use in allograft ACL reconstructions: Two-year clinical results of a MOON cohort study. *Knee* 2013

## PRP and ACL Reconstruction

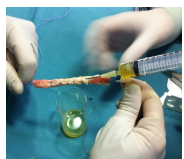
Donor-site Morbidity

**Methods**

- RCT, 40 patients,
- Effect of the addition of autologous PRP gel sutured into the patellar and tibial bone plug harvest site

**Results**

- 12-month FU
  - VAS scores → not significantly different
  - VISA scores (validated to quantify knee function in subjects with patellar tendinopathy) → significantly higher in patients treated with PRP  $P = 0.041$



Usefulness of PRP in reducing subjective pain at the donor-site level

Carnello et al. Autologous platelet-rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: A randomized, controlled clinical study. *Knee Surg Sports Traumatol Arthrosc* 2012

## PRP and ACL Reconstruction

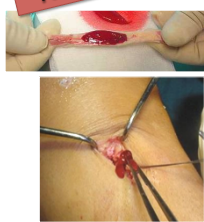
Graft maturation  
Tunnel healing

**Purpose**

To evaluate the clinical and inflammatory parameters with the addition of platelet-derived growth factors (PDGF) in primary ACL reconstruction with B-PT-B allograft.

**Methods**

- Prospectively randomized, 100 patients
- Arthroscopic B-PT-B allograft ACL-R (n=50) vs a group in whom platelet-enriched gel was used (n=50).
- The platelet concentration was  $837 \times 10^3 / \text{mm}^3$
- The gel was introduced inside the graft and in the tibial tunnel.




Valenti JR et al. Has Platelet-Rich Plasma Any Role in ACL Allograft Healing? *Arthroscopy* 2009

## PRP and ACL Reconstruction

**Results**

- No differences in the number of associated injuries
- No statistically significant differences between the groups for
  - inflammatory parameters (knee perimeter and C-reactive protein level)
  - MR imaging appearance of the graft
  - clinical evaluation scores (VAS, IKDC, and KT-1000)



Valenti JR et al. Has Platelet-Rich Plasma Any Role in ACL Allograft Healing? *Arthroscopy* 2009

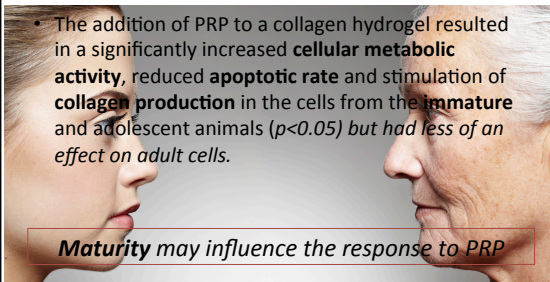
# What does it mean ???

## Controversial or Unsolved Issues

- PRP contains cell types with potentially effects in tissue healing
  - WBCs** → monocytes and polymorphonuclear neutrophils may trigger a localized inflammatory effect (critical to the tissue repair process)
  - Neutrophils** → have been hypothesized to impede healing<sup>1</sup>
- Thrombin and/or calcium chloride is necessary to catalyze the conversion of fibrinogen to fibrin
  - Also induces platelets to secrete growth factors
    - Exogenous thrombin activation of PRP may actually diminish its ability to induce bone formation compared with non-thrombin-activated PRP<sup>2</sup>

1. DeLong et al. Platelet-rich plasma: The PAW classification system. *Arthroscopy* 2012  
2. Han et al. The effect of thrombin activation of platelet rich plasma on demineralized bone matrix osteoinductivity. *J Bone Joint Surg Am* 2009

### Controversial or Unsolved Issues



- The addition of PRP to a collagen hydrogel resulted in a significantly increased **cellular metabolic activity**, reduced **apoptotic rate** and stimulation of **collagen production** in the cells from the **immature** and adolescent animals ( $p < 0.05$ ) but had less of an effect on adult cells.

**Maturity may influence the response to PRP**

Cheng et al. The Effects of Age and Platelet-Rich Plasma on ACL Cell Viability and Collagen Gene Expression J Orthop Res. 2012

### Controversial or Unsolved Issues


- What's the most efficacious platelet concentration for tissue healing → still unknown
  - $1.5 \times 10^6$  platelets per microliter<sup>1</sup>
- The absence of a validated classification system that identifies differences between PRP formulations (activation mechanism, platelet number, and cell content) makes it difficult to compare studies
  - two classifications systems recently proposed<sup>2,3</sup>

1. Giusti et al. Identification of an optimal concentration of platelet gel for promoting angiogenesis in human endothelial cells. Transfusion 2009  
2. Gilling et al. Platelet-rich plasma: The PRP classification system. Arthroscopy 2012  
3. Mishra et al. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol 2012

### Controversial or Unsolved Issues

#### Cost-benefit

- USA → The market for PRP, valued at \$45 million in 2009, is expected to grow to \$126 million by 2016.



GlobalData: Platelet Rich Plasma: A Market Snapshot. Available at: <http://www.docstoc.com/docs/47503668/>

### Summary

- The addition of platelet concentrates to ACL reconstruction may have a beneficial effect on graft maturation and could improve it by **20-30%** on average, but with substantial variability
- The most likely mode of action is that treatment accelerates graft repopulation and remodelling
- The current evidence also shows a **very limited influence** of platelet concentrates on graft-bone interface healing and no significant difference in clinical outcomes

### Take Home Message

- There is need for standardisation of PRP preparation methods and conduct good research.
- There is currently insufficient evidence to support the routine use of PRP for treating ACL injuries.

Moraes et al. Cochrane Database Syst Rev. 2013



**Thank you**



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