



Platelet Rich Plasma: rationale & evidence for use in the joint

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Outline

- What is PRP?
- Driving forces
- Processing
- Rationale for use in the joint
- Evidence
- Clinical Recommendations

Current level of use

- Marked increase in joint use last 3-5 years. Previously a soft tissue treatment
- Difficult to calculate due to different devices and other uses of PRP
- Estimate: U.S. 1000's: world wide 10,000's

Driving forces

- Company marketing
- Professional athletes i.e. Tiger Woods and other testimonials
- Expanding drug and medication rules
- Safety Profile
- Supportive scientific research: on-going

Platelet Rich Plasma

Defined as *any* plasma product with a platelet count higher than whole blood.

- Numerous Devices
- Variable levels of WBCs, PLTs, & RBCs
- No industry standards in procurement or scientific reporting

Devices

- Large Spectrum: all PRP is not the same
 - Test tubes & tube kits
 - Filters (devoid of plasma)
 - Complex automated systems with CPUs.
- Marketing and sales driven, very few companies produce any useable scientific data for horses
- Much of the research is biased towards a specific proprietary device or process

Mechanism of Action

Over 200 growth factors and proteins

- Platelet derived growth factors:
 - PDGF, TGF- β , HGF, VEGF
- Plasma derived growth factors:
 - IGF
- Fibrin matrix:
 - Fibrin associated proteins anabolic to healing
- Monocytes?
 - Mediate the healing/inflammatory response

Transforming Growth Factor- β 1 Stimulates Articular Chondrocyte Proteoglycan Synthesis and Induces Osteophyte Formation in the Murine Knee Joint

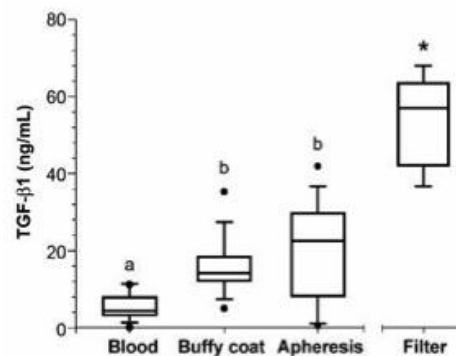
HENK M. VAN BEUNINGEN, PETER M. VAN DER KRAAN, ONNO J. ARNTZ, AND WIM B. VAN DEN BERG

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Mice

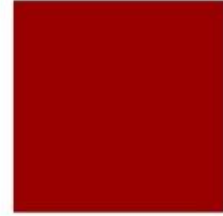
- 0.1 μ g TGF- β 1 IA Three doses in the stifle
- Inflammation & osteophyte formation
- 0.1 μ g=100ng

PRP in horses



Sutter et al, AJVR 2004

Understanding PRP



Platelet Concentration

Clinically you want to know dose: concentration irrelevant unless you know volume of PRP.

Rule of thumb: the less volume of blood processed the less platelets. Recovery of most systems 60-70% at 10% of the whole blood volume.

Platelet dose: math



Example Case

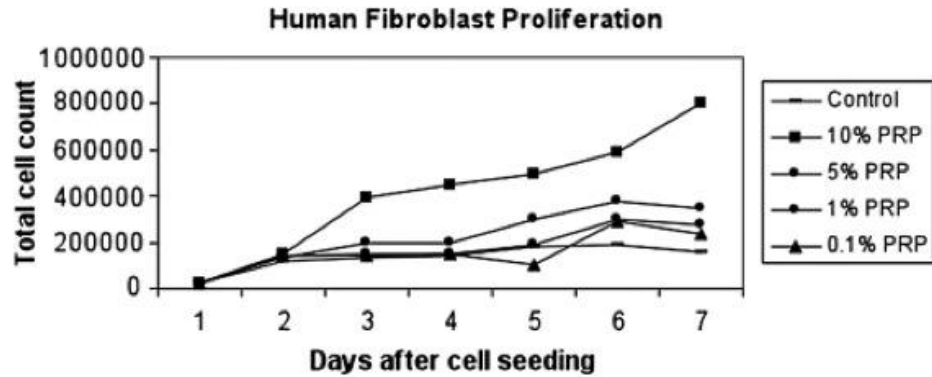
Baseline count 100,000/ul

7x=700,000/ul. 4ml @ 700,000,000/ml= 2.8×10^9 PLT

5x=500,000/ul. 6ml @ 500,000,000/ml= 3.0×10^9 PLT

Dose dependent response

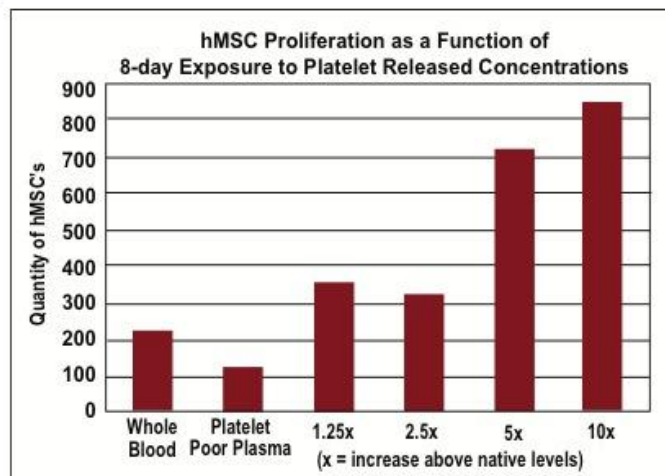
How many platelets are needed?



[Tissue Eng Part C Methods. 2009 September; 15\(3\): 431-435.](#)

Dose dependent response

How many platelets are needed?



Haynesworth SR, Kadidyal S, Liang LN et al. 48th meeting Orthopedic Research society

Clinical Platelet Dose



- Optimum dose unknown
- Tissue Specific?
- May partially dependent on other factors not associated with platelet numbers

Understanding PRP

Leukocytes

- Most devices concentrate leukocytes
- Most devices can be modified to reduce leukocytes usually at the expense of platelets
- Exceptions: Harvest® (horses only), tube or syringe devices/kit that collect portion of buffy coat and all of the PPP.
- **No** clinical evidence of deleterious/pro-inflammatory response in the joint

Leukocytes

Leukocytes are **not** necessarily concentrated proportionately to whole blood.

	Baseline	BC-PRP	Fold Incr.
WBC	4.6 (0.9)	14.3 (3.6)	3.1
Basophils	0.04 (0.01)	0.04 (0.01)	0
Lymphocytes	1.9 (0.5)	8.5 (2.6)	4.47
Monocytes	0.5 (0.2)	1.09 (0.9)	2.18
Neutrophils	2.1 (0.7)	4.9 (1.2)	2.3

Everts PAM, Transfus Med. 2006;16 363-68

RBC Contamination

Some RBC contamination in most PRP, superficial layer of RBC usually taken to maximize platelet count.

- In-vitro profound effect on chondrocyte metabolism
- In-vivo appears to be mitigated by the joint. Normal after 10wks.

Hooiveld et al: Blood induced joint damage, J Rheumatol, 2003

- Physiologic, supraphysiologic concentrations appear to stabilize the clot in collagen gels. Sustained GF release? Not tested clinically

Harrison et al: Journal of Orthopaedic Research, 2010

Rationale (theoretical) for use in the joint

- Anti-inflammatory
- Promotes soft tissue healing
- Promotes cartilage healing directly
- Promotes cartilage healing via synovium

Evidence: Anti-inflammatory

Mechanisms

- Inhibits monocyte/macrophage release of inflammatory mediators.
- Lipoxins (LXA₄) specifically reduce inflammation by inhibiting recruitment and encouraging apoptosis of neutrophils

El-Sharkawy, et al. J periodontol 2007. 78(4) 661-69

- HGF-hepatocyte growth factor, TGF- β also anti-inflammatory

Bendinelli, et al. J Cellular Physiology 2010

Evidence: Anti-inflammatory

Clinical Evidence

Soft tissue: numerous studies suggesting clinical improvement (decreased pain & inflammation) in surgical wounds, tendon and ligament injuries.

Joint: Several active human studies. Few published

IA PRP for Knee OA

- Kon et al., Knee surg sports Traumatol Arth (2010): 6-12 month follow up
- Filardo G & Kon E et al., Knee surg sports Traumatol Arth (2010): 2yr follow up
- Kon et al., AAOS abstract (2011) Cohort study comparing HA & and PRP.
- Sanchez M & Antitua, Clin Exp Rheumatology(2008) IA injection of PRGF

Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions

Elizaveta Kon · Roberto Buda · Giuseppe Filardo · Alessandro Di Martino · Antonio Timoncini · Annarita Cenacchi · Pier Maria Fornasari · Sandro Giannini · Maurilio Marcacci

Patient Selection

- n=100 Chronic Knee Pain (4 months or longer) and OA evidence radiographically or MRI.
- n=27 previous surgery
- n=58 identified chondral lesions

Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis

Giuseppe Filardo · Elizaveta Kon · Roberto Buda · Antonio Timoncini · Alessandro Di Martino · Annarita Cenacchi · Pier Maria Fornasari · Sandro Giannini · Maurilio Marcacci

- Double spin tube protocol:
 - 150ml of blood processed:
 - 6x platelets, WBC not reported
 - 5ml dose
- Activated with 10% CaCl.
- 3 treatment q21 days. WBC, RBC not reported.

Results

- No major adverse events
- Significant improvement in IDKC objective and subjective clinical scores
- Only 3/10 older patients with severe arthritis improved.
- Greatest improvement young patients with lower degrees of arthritis.
- Previous surgery no difference.
- Median duration of clinical improvement 9 mos. Significantly less at 12 mos compared to 6 mos.

PRP vs. HA

- Cohort study (n=60): three weekly injections of either PRGF or Hyaluronic acid.
- Matched groups in terms of severity: outcomes using the WOMAC & physical function scale
- At 5 wks significantly better improvement with PRGF.

Sanchez et al. Clin Exp Rheumatology (2008)

PRP vs. HA

- Cohort study (n=150): three injections at 21d intervals either PRP or HA (1 group HMW & 1group LMW).
- Subjective and objective IDKC at 6 months
- No significant difference HA groups, significant improvement with PRP when compared to HA groups (duration of clinical improvement & IDKC scores).

Kon et al, AAOS annual meeting, proceedings (2010)

Soft Tissue

- Several clinical studies evaluating PRP as an adjunct to ACL & rotator cuff surgery. Mixed results.
- Meniscus
 - In-vitro.
 - Rabbit model with surgical defects.

Ishida K et al, Tissue engineering 2007

Cartilage healing

In vivo: appears to have an anabolic effect on chondrocytes.

Animal Models: appears to improve healing in surgical cartilage defects: does not grow significant hyaline cartilage.

Summary: Evidence vs. Claims

- Useful for treatment of joint sepsis: no evidence
- Heals chips, OCD lesions or Cysts: no evidence
- Slows progression of arthritis: low level evidence
- Promotes cartilage healing: low level evidence
- Promotes soft tissue healing in joint: low level evidence
- Anti-inflammatory: moderate evidence
- Safety: high level evidence

Contraindications

- Infection especially *Pseudomonas*, *Enterococcus* and *Klebsiella*. *Septicemia*.
- Inability to adhere to aseptic technique
- Recent treatment with NSAIDs? 48hrs?
- Recent corticosteroid treatment?

