Efficacy of Platelet Rich Plasma and Shock Wave Therapy

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

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Platelet-rich plasma PRP

- Platelet-rich in growth factors
- Plasma rich in growth factors
- Platelet-rich fibrin matrix
- Platelet-rich fibrin
- Fibrin sealant
- Platelet concentrate

- Originally used in clinical practice as and adjunct to surgery (oral) to assist in the healing of various tissues.
- Also use in prosthetic surgery to promote tissue healing, implant integration and control blood loss.
- PRP has also been used at the time of surgery involving shoulder, hip and knee joints
- Used to improve bone healing

Basic science

- PRP may be defined as a volume of plasma fraction of autologous blood having a platelet concentration above baseline, and is therefore a concentrated source of autologous platelets.
- PRP is prepared from a volume of autologous blood using extracorporeal blood processing techniques such as blood savers/separators, centrifuges and filtration methods.
- PRP may contain variable concentrations of red and white cells depending of the preparation technique

Platelets

- Cytoplasmatic fragments of megakaryocytes formed in the bone marrow.
- Smallest of the blood components, irregular shape, diameter 2-3µm.
- Lack nuclei
- Contain organelles
- The types of granules: α,δ,λ

α granules

- Membrane
- 200 – 500 nm
- 50-80 granules per platelet
- Contain more than 30 bioactive proteins

Table 2 Growth factor release and their possible roles

Growth factor	Effect
Platelet-derived growth factor	Angiogenesis, macrophage activation Fibroblasts: proliferation, chemotaxis, collagen synthesis Enhances the proliferation of bone cells
Transforming growth factor-β	Fibroblasts proliferation Synthesis of type I collagen and fibronectin Induce deposition of bone matrix, inhibits bone resorption
Platelet-derived epidermal growth factor	Stimulates epidermal regeneration Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts Enhances the production and effects of other growth factors
Vascular endothelial growth factor	Vascularisation by stimulating vascular endothelial cells
Insulin-like growth factor 1	Chemotactic for fibroblasts and stimulates protein synthesis Enhances bone formation
Platelet factor 4	Stimulate the initial influx of neutrophils into wounds Chemoattractant for fibroblasts
Epidermal growth factor	Cellular proliferation and differentiation

Table 1 Names of production devices and products

Technology summary	Device name	Name of product	Increase in platelet no per ml above baseline	Platelet recovery (%)	Prepared product content
Floating buoy or shelf	Biomet GPS	PCP	3.2×	70	Buffy coat product: concentrated platelets, WBC
	Harvest	PRP	4.6×	72	fractions and minimal amount of RBC
	SmartPrep2		4.0×		
	BMACDepuy		4.0×		
	Symphony II				
Cell-saver-based systems	Electa, Haemonetics, CATS, BRAT	PRP	4–6×	75	Platelet concentrate only
Computer aided system	Sorin Angel	PRP	4.3×	70	Buffy coat product: concentrated platelets, WBC
	Arteriocyte Medical (Magellan)	PRP	5.1×	76	fractions and minimal amount of RBC
Standard centrifugation	Autologel system Smart PReP	PRP	1–2×	78	Platelet in plasma suspension with minimum white cells and low concentration of platelets
	Cascade PRFM fibrinet system	PRFM	1–2×	78	Platelet-rich fibrin membrane
	Choukroun's PRF	PRF	1–2×	70	Leucocyte and platelet rich fibrin
Direct siphoning	Genesis CS	PRP	6×	68	concentrates of platelets, leucocytes through siphoning device
Direct aspiration	Secquire	PRP	1.6×	31	Manual aspiration of platelet and plasma after centrifuging
	Arthrex ACP	ACP			
Platelet separation	Vivostat	PRF	6×	65	Platelet-rich fibrin
		Fibrin sealant			Fibrin sealant without platelet
Platelet filtration	Caption	Platelet concentrate	4.3×	–	Concentrated platelets without plasma

Muscle Injuries

- While the use of recombinant growth factor for muscle injuries has a strong theoretical and scientific basis, cost and side-effects may contraindicate their use
- Whereas anecdotally being widely used in elite sport, the use of PRP for acute muscle injuries has little scientific support with very few studies.
- At present there is little scientific support for the use of PRP for the management of muscle strain injuries.

Hammon et al 2009

100 µl of PRP repeatedly injected into rat tibialis anterior artificially injured.

- Functional improvement
- Elevated myogenesis

Unknwon transferabilit to humans

Provides some support for the use of PRP in promoting muscle injury regeneration.

Wright-Carpenter et al 2004

Autologous Conditionated Serum (ACS):

Compared return to play of 18 proffessional athletes treated with 5 ml PRP vs 11 treated with traumeel and actovegin.

Reduction on RTP (16 vs 22 days).

Concerns: choice of control, lack of blinding, potential bias of the MRI.

Case reports:

Loo et al 2009

Serial use of PRP on 35 y proffessional body-builder US confirmed adductos longus injury

Hammilton et al 2010

Single injection of a grade II semimembranosus muscle strain injury rapid resolution, both clinical and at MRI.

Sanchez et al 2010

21 muscle injuries of various anatomical localitation on Spanish footbak proffessional players of "La Liga"

Control: matched players aged 25 treated previously with other treatments 1-3 injections + Physiotherapy

Reduced pain, swelling and RTP.

Lacking methodological details.

Some Unanswered Questions Regarding the Use of PRP in Muscle Strain Injuries

- Does PRP reduce recovery time from muscle strain injury?
- **What are the indications for PRP utilization?**
- Which are the active GFs in a PRP solution?
- How do the GFs interact with each other in an acute or chronic injury?
- **Is timing of application important?**
- **What concentrations/volumes of PRP are required?**
- **How many applications of PRP are optimal?**
- Does the platelet concentration really matter?
- Does the system utilized matter?

Hamilton B Best TM Clin J Sport Med 2011

Some Unanswered Questions Regarding the Use of PRP in Muscle Strain Injuries

- **Do you need to activate the PRP before application?**
- Should you aim to exclude all white cells?
- Is whole blood just as effective?
- What is the role of exercise and rehabilitation after PRP infiltration?
- **What are the short-term and long-term side effects of PRP?**
- Is there a supraphysiological performance enhancing effect of PRP infiltration in muscle?

Hamilton B Best TM Clin J Sport Med 2011

Tendinopaties

Table 4 Studies on platelet-rich plasma and tendinopathy

Reference	Level of evidence	Tendon	Patients (n)	Follow-up	Outcome	Complications
Peerbooms et al[71]	Prospective randomised study (level I)	Elbow extensor or flexor tendon	100	52 weeks	DASH score improved in both groups, but sign. much more in the platelet-rich plasma group	No
De Vos et al[72]	Prospective randomised study (level I)	Achilles tendon	54	24 weeks	Mean VISA-A score improved in both groups; however, no significant group differences	No
Randelli et al[73]	Prospective randomised study (level I)	Rotator cuff tendon	55	104 weeks	Significantly better external rotation strength, and higher SST, UCLA, constant scores 3 months after surgery, but no group differences after 2 years (only for subgroups)	No
Castricini et al[74]	Prospective randomised study (level I)	Rotator cuff tendon	88	65 weeks	No significant difference in total Constant Score or in MRI tendon score PRBM	No
Mishra & Pavelko[75]	Prospective cohort study (level II)	Elbow extensor or flexor tendon	20	25.6 months (12–38 months)	Reduction in visual analogue pain score (93% of treated patients)	No
Filardo et al[68]	Prospective cohort study (level III)	Patellar tendon	31	6 months	Significant improvements in Tegner score, EQ-5D VAS score and pain level	No
Gaweda et al[65]	Case–control study (level III)	Achilles tendon	14	18 months	AOFAS scale improved from 55 to 96 points VISA-A scale improved from 24 to 96 points	No
Sánchez et al[67]	Case–control study (level III)	Achilles tendon	12	32–50 months	Earlier regain of ROM, and less time to start running and training	In the control group (wounds)
Kon et al[69]	Cohort study (level IV)	Patellar tendon	20	6 months	Improvements in Tegner, EQ-5D VAS and Short Form (36) Health Survey scores	No

- Difficult to formulate indications in tendon injuries in a clinical setting based on the available scientific.
- There is a lack of well designed studies to support the use of PRP in clinical setting in the clinical management of tendon injuries.
- For each individual athlete and circumstance, a risk/benefit analysis should be performed before embarking on this as yet scientific unproven therapeutica modality.

Cartilage and articular tissues

Table 5 Studies on platelet-rich plasma (PRP) and intra-articular lesions

Reference	No	Study design	Inclusion criteria	Intervention	Control group	Primary outcome measures	Follow-up (months)	Outcome intervention group (percentage improvement)	Outcome control group (percentage improvement)
Dragoo *et al*[62]	108	RCT (level I)	ACL tear	PRP clotted around the graft and ACL reconstruction with bone plug	ACL reconstruction without PRP	MRI	3.6	Graft signal intensity 6 m: 100% mature with PRP, 92% mature with PRP + BP	Graft signal intensity 6 m: 78% mature with control, 69% mature with control + BP
Radice *et al*[12]	50	Case control trial (level III)	ACL tear	PRP in a synthetic gelatin sutured on the ACL graft	ACL reconstruction without PRP	MRI	6	Homogeneity: 1.1 (0–4)	Homogeneity: 3.3 (0–4)
Sánchez *et al*[10]	60	Case control trial (level III)	Knee OA	Three PRP injections	Hyaluronan injections	WOMAC	5 weeks	Pain subscale success: 34%	Pain subscale success: 10%
Silva *et al*[61]	40	Case control trial (level III)	ACL tear	PRP in femoral tunnel PRP in femoral tunnel and intraarticular at 2–4 weeks PRP activated with thrombin in femoral tunnel	ACL reconstruction without PRP	MRI	3	NA	NA
Kon *et al*[13]	100	Case series (level IV)	Knee OA and cartilage lesions	3 PRP injections	No control group	IKDC subject (0–100) EQ-VAS score (0–100)	12	Mean IKDC score: 40.5 to 62.5 (34%) Mean EQ-VAS score: 50.3 to 69.5 (39%)	–

- These reports on the use of PRP through intra-articular injections suggest good potential in faovouring pain reduction and improved function.
- Methology of studies is questionable
- The best procedure and proper application modalities still need to be defined.
- It is also not known how applicable the results of PRP being used for treating degenerative articular injuries in non-athletes would be for the active Athletic population.

Suggested techniques and postinjection recommendations

- Ultrasound guidance
- No agreement on whether the needle should be place inside tendons
- Evacuate exudates before injecting.
- Emptying the joint of arthroscopy fluid
- Gel and semisolid forms during open surgery
- Preparation and administration under strict asepsis
- No agreement on the concomitant use of NSAIDs and local anesthetics
- Exercise after 2-5 days
- Ice, rest and limb elevation 48h

Potential adverse effects

- To date there is not compelling evidence of any systemic effect of local PRP injection.
- No scientific reports suggesting potential cause-effect relationship between growth factors present in PRP and carcinogenesis.

Research

- Clear inclusion and exclusion criteria: special attention to cofounding factors (use of medication)
- Study population: homogenous, appropriately selected.
- Clear diagnosis of the injury
- Production of PRP
- Delivery of PRP
- Definition of outcome measures and end points: follow up measurements for at least 2 years
- Standardised post-treatment protocol
- Adverse effect documentation
- RCT / Prospective Cohort / Multicentre trials

Antidoping regulations

- Since 2011, PRP is permitted by all routes of administration

Summary and recommendations

- Should we use a treatment with limited evidence supporting its clinical efficacy and with limited evidence supporting its safety?
- Medical ethics
  - Beneficence (doing good)
  - Non-maleficence (do no harm)
  - Patient autonomy (self determination)

Summary and recommendations II

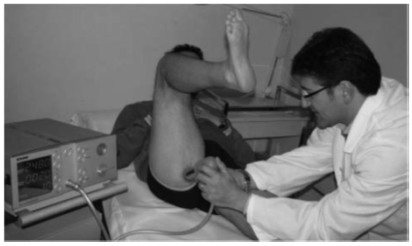
- Non-maleficence is the principal determinant of medical practice
- Beneficence is not proven with PRP
- Current medical ethics generally allows clinicians to make an individual choice to prescribe treatments that have not shown beneficence as long as the treatment is non-maleficent.

Summary and recommendations III

- The final recommendation of the IOC Consensus Group is to proceed with caution in the use of PRP in athletic sporting injuries.
- More work is warranted on the basic science and greater rigor should be implemented in developing robust clinical trials to demonstrate the efficacy or otherwise of PRP.

« A Doctor must be satisfied there is a sufficient evidence base for off-licence prescribing, and pacientes must be given sufficient information about those delivering the medication to be in a position to give informed consent»

General Medical Council UK 2006



Speed C.

Br J Sports Med. 2013 Aug 5. doi: 10.1136/bjsports-2012-091961

- 23 appropriate studies were identified.
- Focused extracorporeal shockwave therapy (F-ESWT) and radial pulse therapy (RPT) should be considered as different treatment modalities.
- There continues to be a lack of large well-designed RCTs in general in F-ESWT and RPT.
- Where benefit has been demonstrated further research into the most effective regimes is needed.

Speed C.

Br J Sports Med. 2013 Aug 5. doi: 10.1136/bjsports-2012-091961

- There is good evidence for:
- Benefit for high-dose focused ESWT (F-ESWT) and for (RPT) in plantar fasciitis.
  - Lack of benefit for low-dose F-ESWT in plantar fasciitis.
  - F-ESWT in calcific tendinopathy of the rotator cuff, especially in high dose.

Speed C.

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There is some evidence for:

- Benefit for high-dose F-ESWT in mid portion and insertional Achilles tendinopathies.
- No benefit in low-dose F-ESWT in this condition.
- Benefit of RPT in calcific tendinopathy.
- Lack of effect of F-ESWT in non-calcific tendinopathy of the rotator cuff and for low-dose F-ESWT in common extensor tendinopathy.

There is no evidence to support not refute the effects of F-ESWT nor RPT in other conditions.

There is mixed evidence for the effects of low-dose F-ESWT in common extensor tendinopathy.

Speed C.

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- It has also been demonstrated over the past few decades that SW is a safe treatment with adverse effects typically being minor, and occurring rarely.
- Where benefit is seen in F-ESWT, it appears to be dose dependent, with greater success seen with higher dose regimes.
- Both treatments offer an alternative to surgery in the management of recalcitrant conditions.