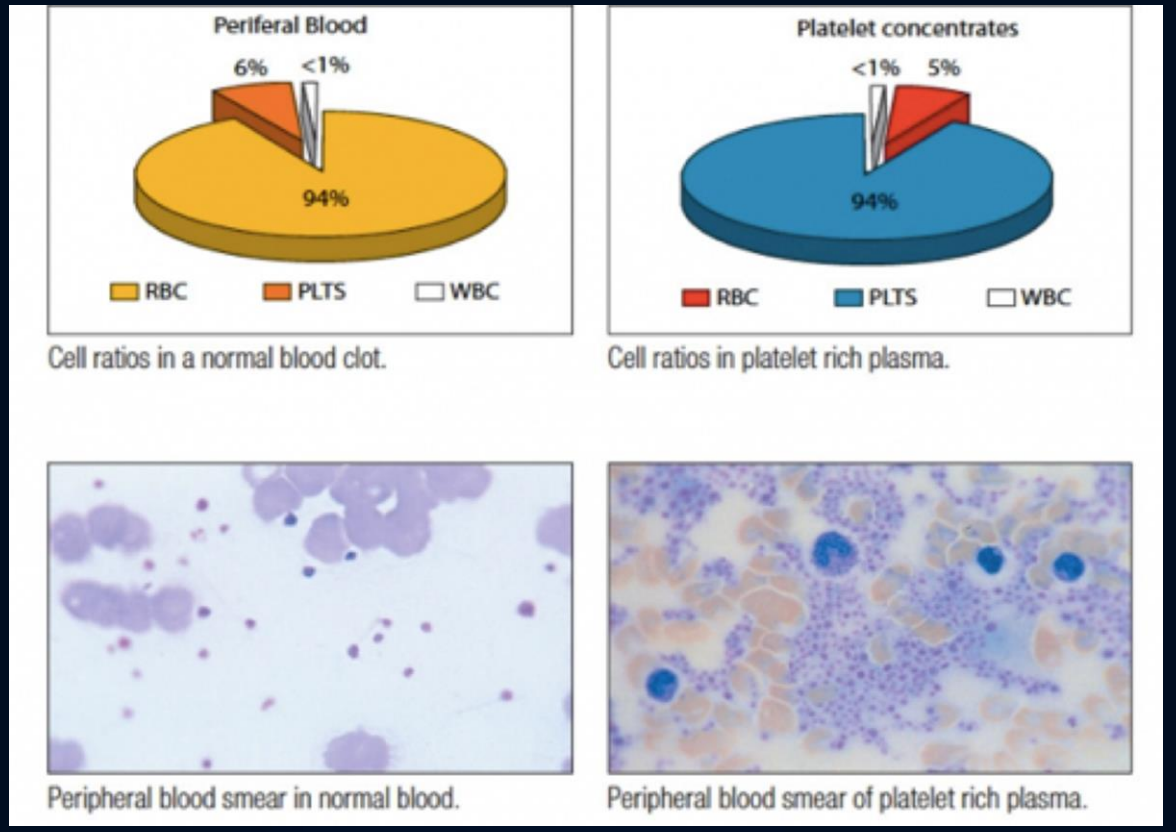
What is PRP?

- Platelet rich plasma (PRP) is a biological means to stimulate wound healing and tissue regeneration by providing growth factors
- A volume of plasma that has a platelet count above that of whole blood
- Platelet count is usually 4-8X that in whole blood



Cell ratios in a normal blood clot.

Cell ratios in platelet rich plasma.

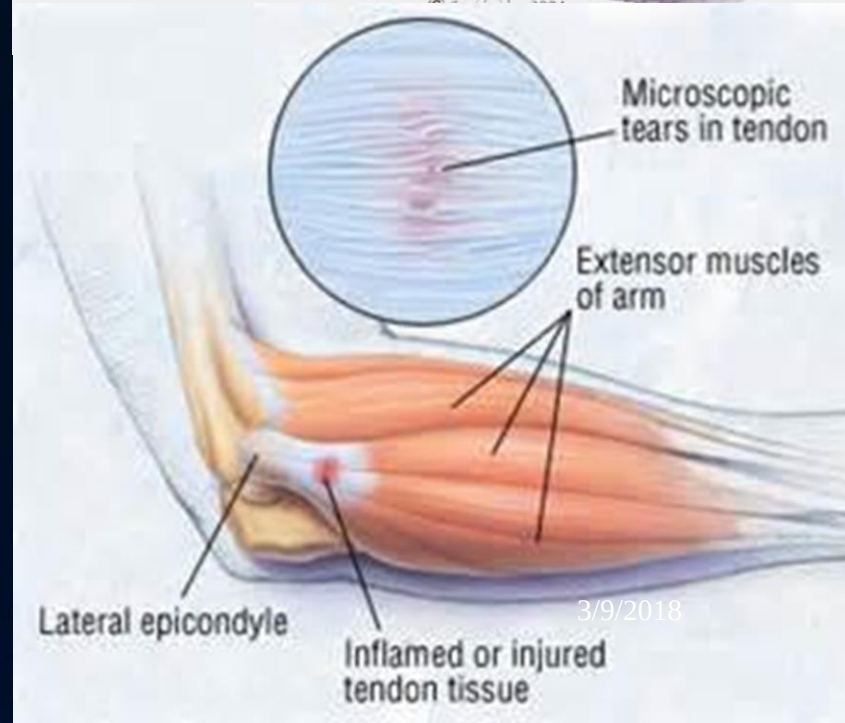
Peripheral blood smear in normal blood.

Peripheral blood smear of platelet rich plasma.

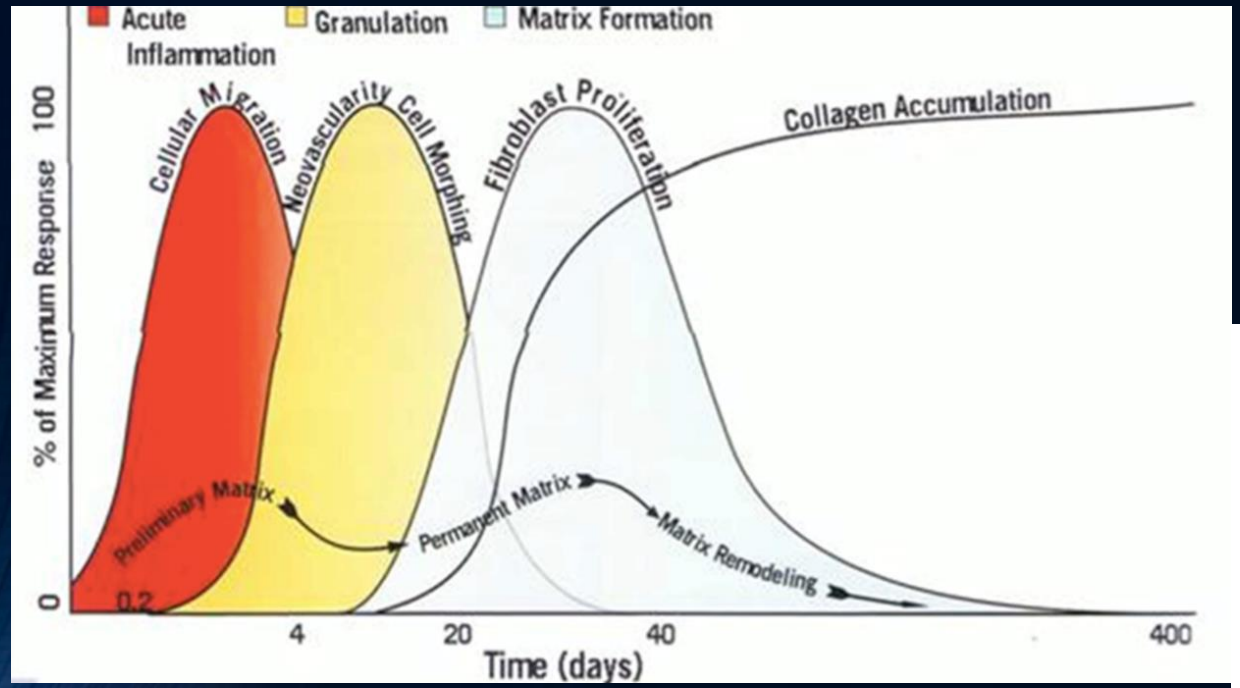
PRP for MSK pain

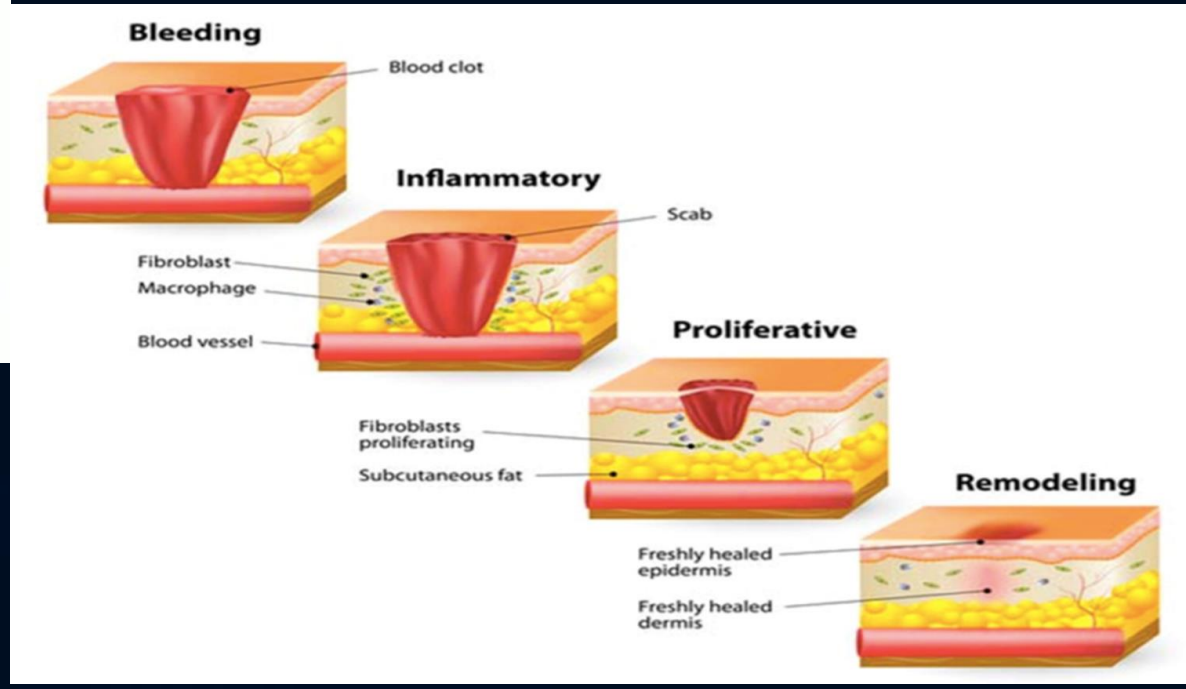
- Initially, PRP was used by orthopedists and sports medicine physicians to stimulate healing of athletic injuries-tendons, ligaments, muscles and bursa

- Later physicians began to study its use for treatment of chronic conditions



Mechanism of Action

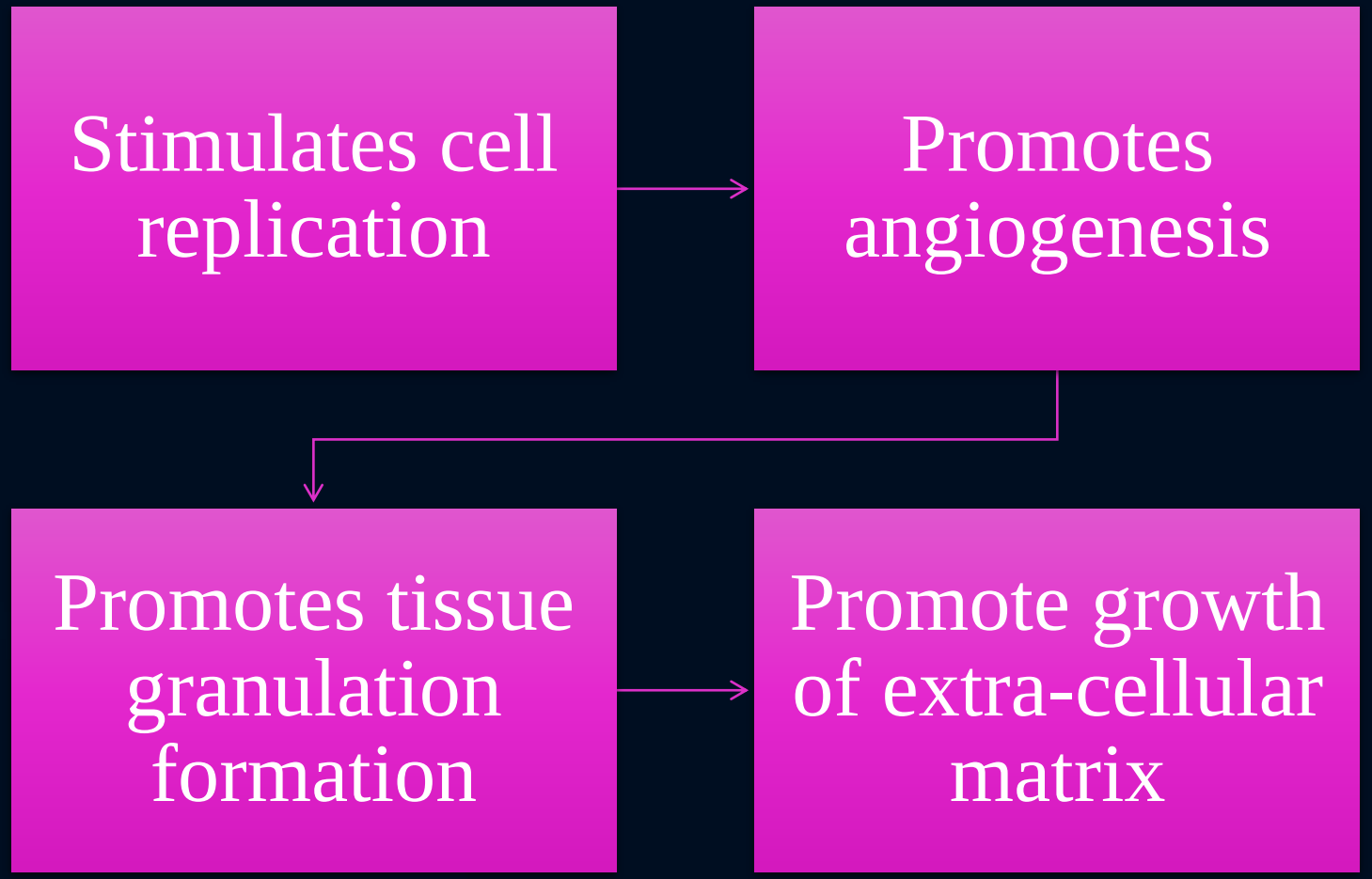




PRP: Growth Factors

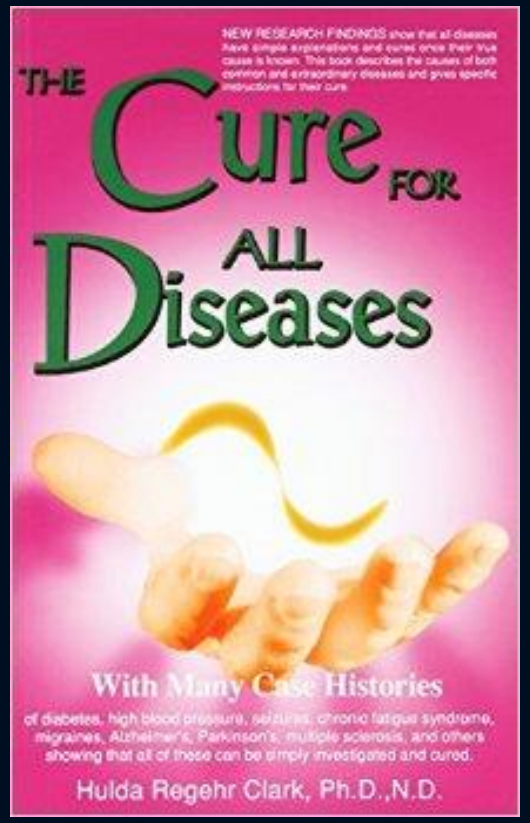
- Insulin-like growth factor (ILGF-1): Mediate growth of skeletal muscle, cell differentiation in repair
- Stromal Cell-derived factor 1-alpha (SDF-1alpha): Supports adhesion/migration of mesenchymal stem and stromal cells
- Bone Morphogenic Protein (BMP): Osteoprogenitor derived cells-promote bone growth
- Growth Differentiation Factor (GDF-5): Chondrocyte, fibroblast and mesenchymal cell expansion
- Platelet derived growth factor (PDGF): Cell replications and angiogenesis
- Transforming growth factor Beta-1 (TGF-Beta1): Stimulate angiogenesis
- Vascular endothelial growth factor (VEGF): Stimulate angiogenesis
- Fibroblast growth factor (FGF): Mediate growth of skeletal muscle, cell differentiation in repair
- Epidermal Growth Factor (EGF): Proliferates ectoderm and mesoderm

Functions of Platelet Derived Growth Factors



Indications

- **Isn’t a cure all, as of yet**
- Tendinitis, Tendinosis, **Osteoarthritis,** Bursitis
- Shoulder, elbow, hip, trochanter bursa
- Entrapment neuropathies
- Enthasopathy, enthesitis (tendons/ligaments attachments)
- Partial muscle tears (not complete tear!)
- Degenerative Disc Disease
- Injection volume: It depends on the target sites:
  - 1. discs 1.5-2 ccs
  - 2. Tendons 2-3 cc (Steroid – peritendinous, PRP –Intra.)
  - 3. Muscle tear – 3-4 cc (Delivered at the site of tear)
  - 4. Major Joints - 5-6 cc
  - 5. Facet and SC joints 0.5-1.0 cc



The Role of Platelet Rich Plasma in the Treatment Algorithm of Knee Osteoarthritis

- Identified 8 studies comparing efficacy between PRP and HA
- 6 prospective RCT
- 2 retrospective
- PRP was superior in 7 studies
- Non-inferior in 1 study

Chart 1: Cohort studies and randomized controlled studies of Platelet rich plasma injections for knee osteoarthritis

Authors	Year published	Study Design	Subjects	Treatment arms	Outcome Measures	Length of follow-up	Adverse effects to PRP Group	Results
Sanchez et al (16)	2008	Retrospective cohort study	60 patients 60 joints	Group A (30 joints), 3x PRP q 1 week. Group B (30 joints), 3x HWHA q 1 week.	WOMAC	5 weeks	No severe adverse events were reported	PRP group with better pain outcomes compared to HA group
Kon et al (17)	2011	Prospective comparative study	150 patients 150 joints	Group A (50 joints), 3x PRP q 2 weeks. Group B (50 joints), 3x HWHA q 2 weeks. Group C (50 joints), 3x LWHA q 2 weeks.	EQ-VAS, IKDC	6 months	No severe adverse events were reported	PRP more effective than HA in patients aged 50 years or younger at 6 months. In patients aged 50 years or younger, PRP and HA showed equal improvements.
Spakova et al (18)	2012	Randomized double blind controlled trial	120 patients 120 joints	Group A (60 joints), 3x PRP q 1 week. Group B (60 joints), 3x HWHA q 1week.	NRS, WOMAC	6 months	No severe adverse events were reported	PRP group with greater improvement in pain and functional outcomes compared to HA group
Sanchez et al (19)	2012	Randomized double blind controlled trial	176 patients 176 joints	Group A (89 joints) 3x PRP q 1 week. Group B (87 joints) 3x HWHA q 1 week.	Responders (50% pain reduction), WOMAC	6 months	No severe adverse events were reported	PRP group had more responders (50% pain reduction) when compared to HA group
Cerza et al (20)	2012	Randomized comparative trial	120 patients 120 joints	Group A (60 joints) 4x PRP q 1 week. Group B (60 joints) 4x HWHA q 1 week.	WOMAC	6 months	No severe adverse events were reported	PRP group with a longer duration of improvements when compared to HA group
Filardo et al (21)	2015	Randomized double blind controlled trial	183 patients 183 joints	Group A (94 joints) 3x PRP q 1 week.	EQ-VAS,IKDC, KOOS, Tegner	12 months	No severe adverse events	PRP and HA provided similar pain and functional

Harvesting PRP

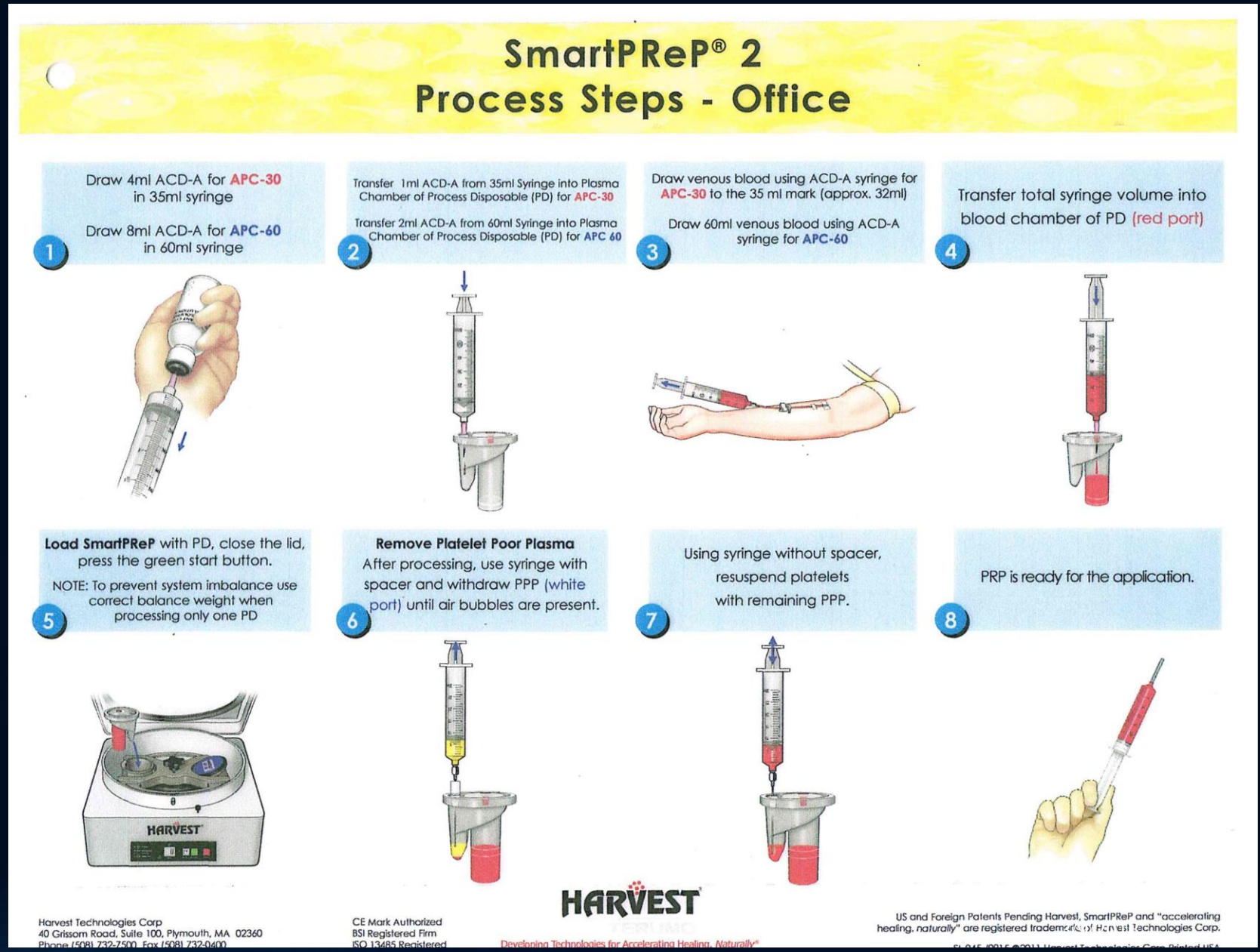
- Strict sterile precautions: from peripheral blood drawing to PRP injections

<u>Anticoagulation:</u>

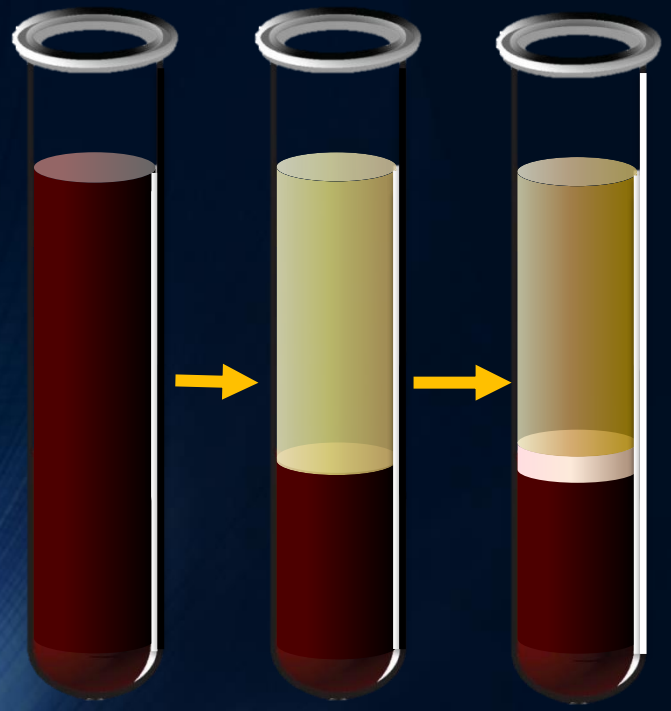
- Not a must if it is done within the time required for coagulation
- It must preserve functional capacity, cellular integrity and morphology (e.g. EDTA may injury the platelet)
- Acidic pH and low extracellular iCa can affect platelet aggregation
- The best is ACD-A: pH is 7.8

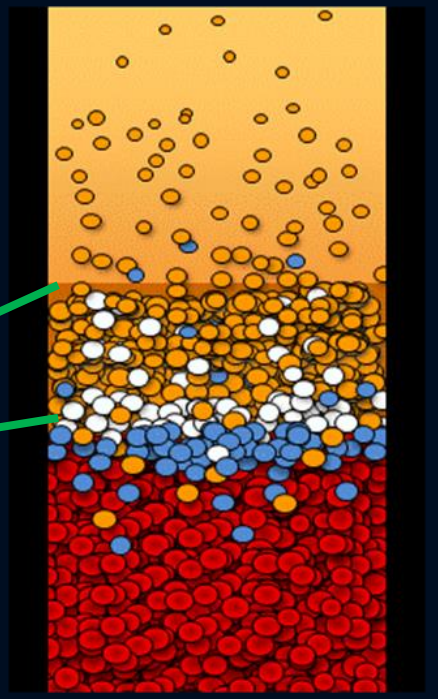
Harvesting PRP

- A typical solution if made from 50 ml of venous blood and 10 ml of anti-coagulant
- 60 cc solution makes 6 cc of PRP
- Produces a product that has 4-6 x the baseline level of platelets
- Newer systems can concentrate platelets up to 7-9 x
- Platelet count of 1-2 million per/ml is considered optimal to promote tissue healing
- Counts above 3 million platelets may actually inhibit wound healing
- Systems that produce platelet concentrations of < 500,000 are no better than platelet poor plasma



Dual spin PRP – the buffy coat





Limitations of PRP Therapy

- PRP solutions are not uniform
- Manufacturers have created proprietary systems using different centrifugation protocols and collecting systems
- These systems produce significantly different PRP solutions as final products
- Success of the procedure can be influenced by the make up of the PRP
- Clinical trials evaluating efficacy are difficult to assess because a standardized protocol for preparation does not exist
- Present data: 50-50% leaning more towards favorable

The highest platelet concentration and yield as compared to 12 other PRP systems, as shown by the data below.

Device	Mean Platelet Count (10^6/mL)	Mean Platelet Yield (Percentage)	Reference
Harvest Technologies	1,027	66.7	Harvest Technologies, "The Composition of PRP Produced from 5 Major PRP Devices: A Comparison Study." 2013 presentation, SL161, unpublished raw data. Request the article
Arteriocyte Magellan®	934	60.1	
Cytomedix™ Angel® System (Arthrex)	677	44.7	
GenesisCS PRP	494	35.5	
RegenKit	97	33.0	
Harvest Technologies	1,215 ± 413	N/A	Kochan A, et al., "Platelet-Rich Plasma Preparation: A Comparison of the Harvest® SmartPReP® 2 Multicellular Processing System APC+® with the Arteriocyte Magellan®." 2009, unpublished raw data. Request the article
Arteriocyte Magellan	1,116 ± 363	N/A	
Harvest Technologies	895 ± 204	N/A	Immune Disease Institute, "Platelet-Rich Plasma Preparation: A Comparison of the SmartPrep 2 System APC+ with the Arthrex ACP™." 2009, unpublished raw data. Request the article
Arthrex ACP® System	365 ± 111	N/A	

Harvesting PRP

13

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- 60 cc solution makes 6 cc of PRP
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- Counts above 3 million platelets may actually inhibit wound healing
- Systems that produce platelet concentrations of < 500,000 are no better than platelet poor plasma

Variables in PRP Harvesting

- Preparation Method-single vs double spin: Single spin separates RBC's from the buffy coat. Second spin clarifies solution and further concentrates platelets-concentrates platelets to 4-8X

- Needle Gauge: used for blood harvest and injection should be greater than 21 g. Small bore needles (less than 21g) can lyse platelets prematurely releasing growth factors

PRP and RBC

Disadvantages:

- Negative effects on chrondocytes has been established (pH alterations, inflammation)
- Hemophiliacs with recurrent hemarthrosis predictably develop early OA

Advantages:

- Red cell are nitric oxide sinks:
- Nitric Oxide is a potent stem cell stimulant
- Red Cells release iron: Iron is used by cells under stress to survive and function

What is the best PRP ?

- There is evidence that both RBCs and neutrophils (PMN's) may have a negative effect on cartilage. For this reason, LP-PRP may be preferable in treating OA of the knee

- Anti-coagulant Use: One study found that acid citrate dextrose (ACD) was shown to be superior to heparin in maintaining platelet integrity and preventing spontaneous activation

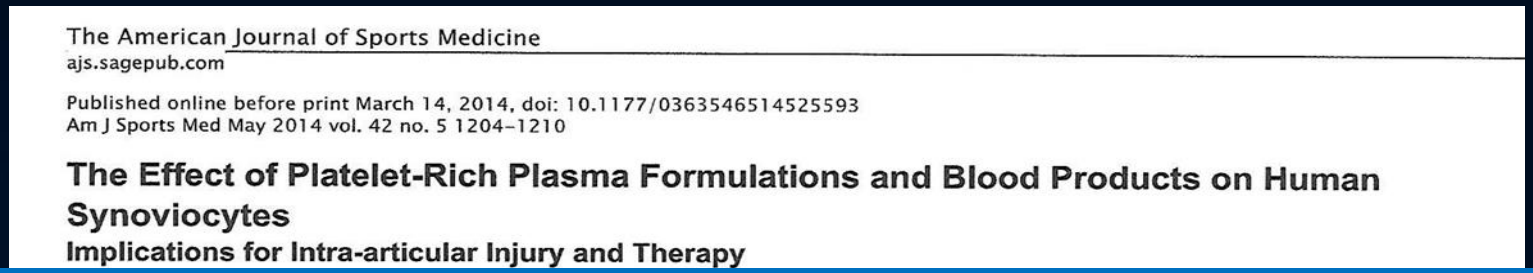
Am. J. Phys. Med. Rehabil. & Vol. 93, No. 11 (Suppl), November 2014

PRP with WBC and RBC

- Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of PRP (Sundman et. al. Am J Sports Med 2012)
- For OA of Knee: PRP with few WBC's and RBC's was superior
- For tendinopathy: Leukocyte Rich PRP solutions may produce better outcome
- PMN Granulocytes (neutrophils) seem to create a catabolic effect
- Mononuclear cells (monocytes and lymphocytes) seem to create an anabolic effect while helping to fight infection
- Peripheral blood mononuclear cells enhance the anabolic effects of platelet rich plasma on anterior cruciate ligament fibroblasts

(J Orthopedic Res. 2013)

PRP with RBCs and WBCs



The American Journal of Sports Medicine
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Am J Sports Med May 2014 vol. 42 no. 5 1204–1210

The Effect of Platelet-Rich Plasma Formulations and Blood Products on Human Synoviocytes

Implications for Intra-articular Injury and Therapy

Conclusion: Treatment of synovial cells with LR-PRP and RBC resulted in significant cell death and proinflammatory mediator production.

Clinical relevance: Consider using LP-PRP and RBC free formulations of PRP for intra-articular use

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Platelet Activation

- Platelet activation prior to injection: this refers to the administration of an exogenous substance to promote more rapid release of growth factors. Typically calcium chloride or thrombin are used for this purpose

- Most authors agree that physiological activation is better

- *Lei H et al. Clin Biochem 2009;42:1452Y60*

Safety profile

- Because the product is derived from the patients own blood, there are no risks usually associated with blood products like transfusion reaction, allergic or immune reaction
- Unlike pharmaceutical products, there are no risks associated with injection of the substance, or drug interaction
- Infection: Strict sterile condition should be maintained throughout, the harvesting and injecting procedures, It was found that PRP has bactericidal effect on Staph and Pseudomonas

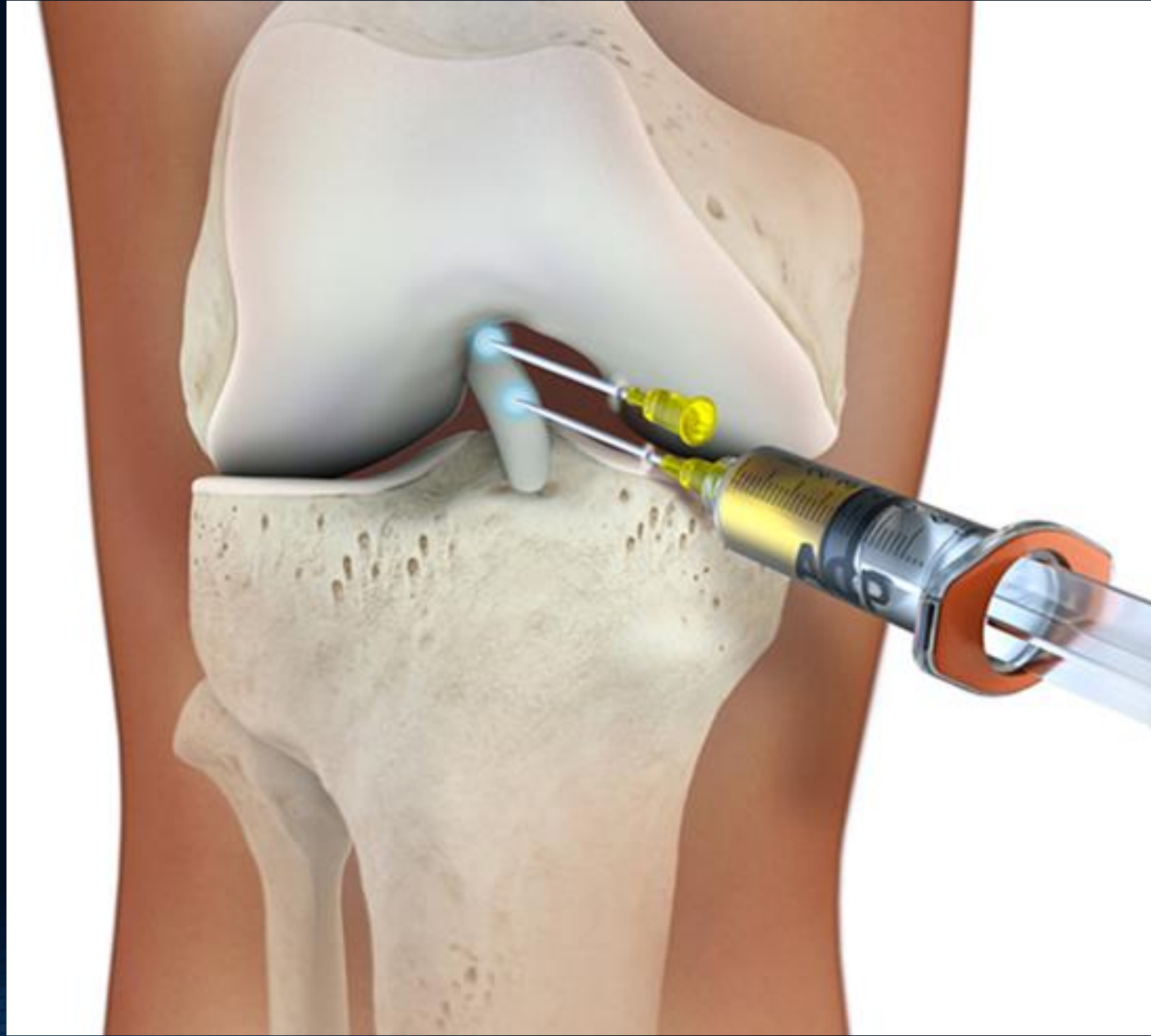
Evidence in literature

Conditions	Level I evidence	Level II Studies
Elbow epicondylitis	yes	
Patellar tendinitis	yes	
Plantar Fasciitis	yes	
Rotator cuff tear	yes	
Annular tear lumbar spine	yes	
Osteoarthritis knee	yes	
Trochanteric bursitis		yes

Dr. Richard Rosenthal slide, recreated

PRP Therapy

- Results take time 3-6 months
- Patients are instructed to rest the injured area for 1-6 weeks
- Patients are then started on a program of physical therapy and re-evaluated after 12 weeks



PRP Procedure Protocol

- NSAID's: have a negative effect on platelet function as they may decrease GF release. Most authors recommend stopping for 5 days before and up to two weeks after injection
- Number of injections: There is no consensus but most authors recommend between 1-3 injections
- Interval between procedures: Weekly, bi-weekly, monthly or quarterly. Note that the growth factors from platelets are released during the first 8 days post injection
- Post Injection Rehab: There are no agreement on post procedure rehabilitation protocols. Authors vary from no restrictions to temporary restriction with gradual return to full activities. Our protocol is 1-2 weeks rest with gradual return to full activity between 6-8 weeks post procedure
- Duration of effect: It varies-severity of disease, healing capacity of patient, age, etc. For knee OA, treatment effect begins to decline 6-9 months post treatment with further loss of benefit at 24 months
- *(Am. J. Phys. Med. Rehabil. & Vol. 93, No. 11 (Suppl), November 2014)*

Leucocyte poor PRP for Knee OA

The American Journal of Sports Medicine
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Am J Sports Med April 2016 vol. 44 no. 4 884–891

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis
An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

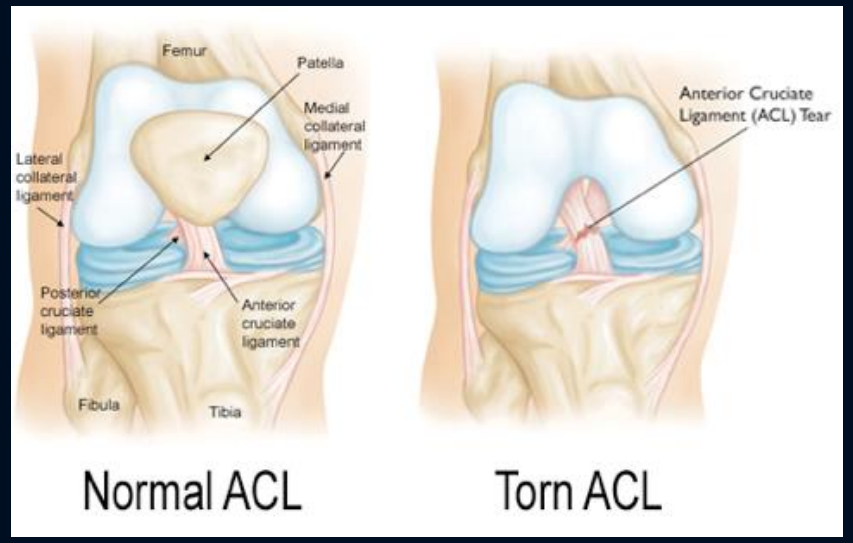
Patrick A. Smith, MD*,†

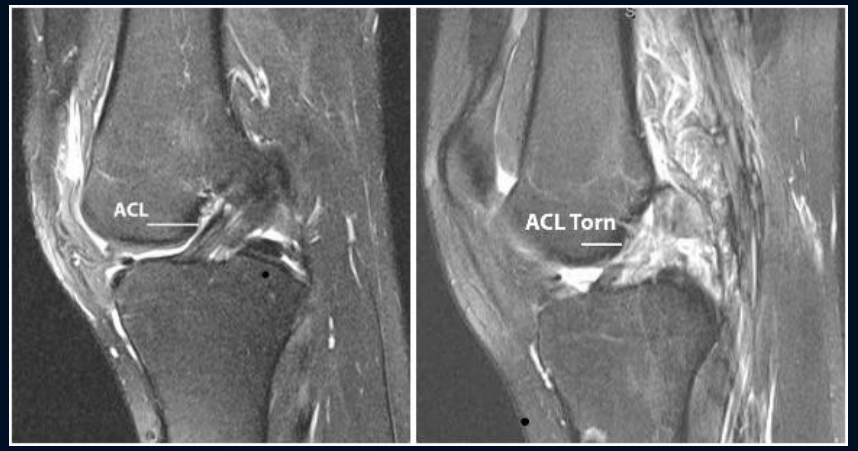
Conclusion: ACP (Leucocytes poor - PRP) is safe and provides quantifiable benefits for pain relief and functional improvement in knee OA. No adverse effects reported with ACP injections.
Other joints with OA may also benefit from this treatment

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
- Results: At 1 year, ACP group had improved score by 78% (saline 7%)

ACL tear

- IV sedation preferred
- 3-4 cc of PRP
- Fluoroscopic or ultrasound guidance
- MiEye arthroscopic device
- Indicated for partial tear only
- Complete tear requires surgical graft
- PRP must be delivered at the site of the tear

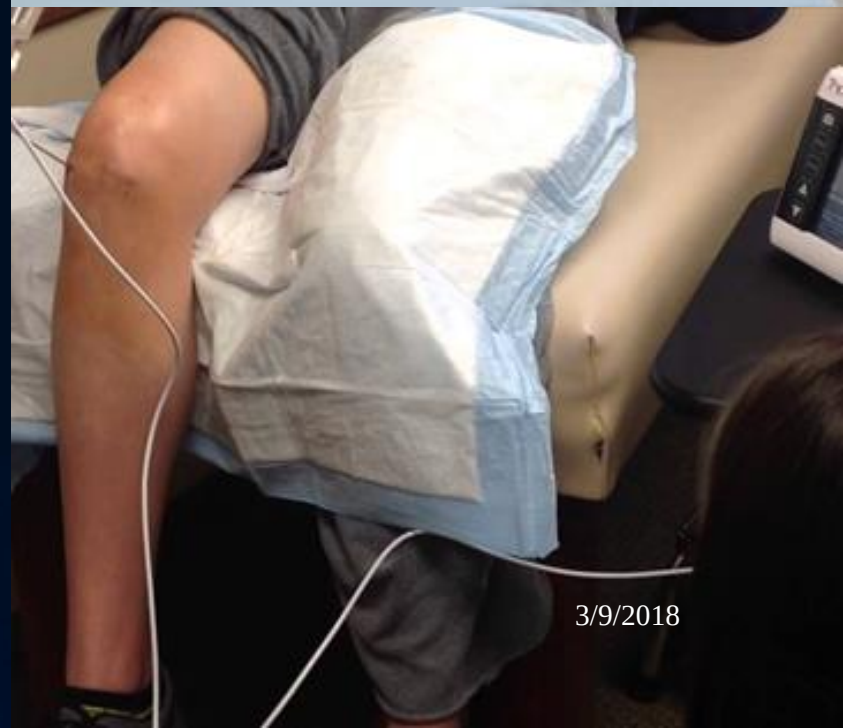




Level of evidence	Author	Diagnosis	PRP Formulation	Results
Double Blind RCT	*Patel AJSM 2013*	*Knee OA*	*leukocyte poor, RBC poor*	*significant difference (vs saline)*
Double blind RCT	*Filardo BMC Musculoskel discord 2012*	*Knee OA*	*leukocyte rich, RBC rich*	*No difference vs saline*
RCT	*Cerza AJSM 2012*	*Knee OA*	*Leukocyte poor, RBC poor*	*Significant difference vs baseline and HA*
Double blind RCT	*Sanchez Arthroscopy 2012*	*Knee OA*	*Leukocyte poor, RBC poor*	*Significant difference vs HA*
Prospective cohert	*Spakova AM J Phy Med Rehab 2012*	*Knee OA*	*Leukocyte poor, RBC poor*	*Significant difference vs HA*
Prospective cohert	*Filardo KSSTA 2012*	*Knee OA*	*Leukocyte rich, RBC rich*	*More pain and swelling with PRP*

MiEye disposable arthroscope

- MiEye is a in-office direct vision diagnostic tool for office set up
- It is a fully disposable, single-use, streamlined visualization device
- Passes thru a standard 14-gauge needle with an integrated camera and light source to perform a diagnostic arthroscopy
- A separate LCD tablet, running on Android OS, is attached via a data cable from the mi-eye needle
- mi-eye is a needle based diagnostic and therapeutic tool, approved by FDA for arthroscopy



Conclusion

- MSK pain has another treatment option
- Low risk, and usually well tolerated
- Fair to good results depending on region, study, and patient
- The future of injectable biologic materials is very exciting
- As the knowledge and control of the mesenchymal stem cells, and PRP contents advances, the treatments options and approaches for MSK pain will change dramatically
- Larger studies with more controlled parameters need to be done, as well as RCTs.

THANK YOU