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Autologous platelet rich plasma therapy in Orthopedics: An update

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Abstract

Recent advances in molecular and nanobiology have led to the identification of specific cytokines that mediate cellular activities which becomes a powerful tool in management of orthopaedic disorders. Platelet rich plasma is a potential "Orthobiologic" agent for treating inflammatory and degenerative musculoskeletal disorders. Platelet rich plasma therapy aimed in rejuvenating the degenerating tissues by neoangiogenesis and neoinnervation thus by increasing the texture and biology of the diseased tissues. This article outlines the guidelines for the usage, precautions, pre and post injection events of autologous platelet rich plasma therapy in musculoskeletal disorders.

Keywords: Platelet rich plasma; Orthobiologic; Growth factors; Transforming growth factor; Centrifugation

Introduction

Platelet Rich Plasma (PRP) is defined as the volume of plasma with an exponential increased platelet concentrations of 5 to 6 times above the baseline (approximately $10^6 - 10^7$ / mL). The rationale for use of platelet rich plasma is to stimulate the biological healing, homeostasis and tissue rejuvenation by a "Supra – Physiological" release of biological micromolecules at the site of treatment [1].

Structure of platelets

During thrombopoiesis, myeloid stem cell forms platelets by fragmentation of cytoplasm with no nucleus and enter systemic circulation. Platelets are found in unactivated form in circulation which retains biconvex discoid shaped with 2–3 μ m in greatest diameter. Platelets get activated when there is a potential insult to the lining endothelium. In normal healthy humans, the ratio of RBCs to platelets ranges from 10 – 20:1 [2].

Zones of platelets

There are four zones of platelets namely.

- Peripheral zone: Glycoprotein rich zone which are required for thrombosis.
- Sol-gel zone: Contains microtubules and microfilaments and allows platelets to retain discoid shape.
- Organelle zone: Rich in α , δ , γ and λ granules
- Membranous zone: M Contains a dense tubular system which synthesizes thromboxane A_2

Growth factors of platelets [2, 3]

Growth factors	Significance
Platelet derived growth factor (PDGF)	Promotes cellular growth and mitosis; neovascularization and neoinnervation; collagen synthesis
Vascular endothelial growth factor (VEGF)	Neoangiogenesis; endothelial cell mitogenicity; increases metalloproteinase activity
Transforming growth factor – β (TGF- β)	Growth of epithelial and endothelial cells at the site of injury; promotes wound healing process by synthesizing collagen.
Fibroblast growth factor (FGF)	Promotes cellular growth; collagen production; regeneration of tissues
Epidermal growth factor (EGF)	Promotes epithelial cell growth; promotes wound healing mechanism; neovascularization

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Platelet Dynamics ^[2]

Once the endothelium is disrupted, platelets interact with micromolecules to achieve hemostasis by following mechanisms

Adhesion

- Endothelial disruption leads to anchoring of collagen and vWF with platelets in the subendothelial layer.
- Binding of GP1b-IX-V receptor with VWF and GP VI receptor and integrin $\alpha_2\beta_1$ with collagen

Activation

- Collagen mediated GP VI signaling, TXA₂ production and PGI₂ inhibition and metabolic flux of platelet eicosanoid pathway converts GP2b/3a receptors to their active form to

initiate aggregation

- Granule secretion
- Morphological change of platelets
- Facilitation of coagulation by phospholipid interaction between platelets and coagulation cascade

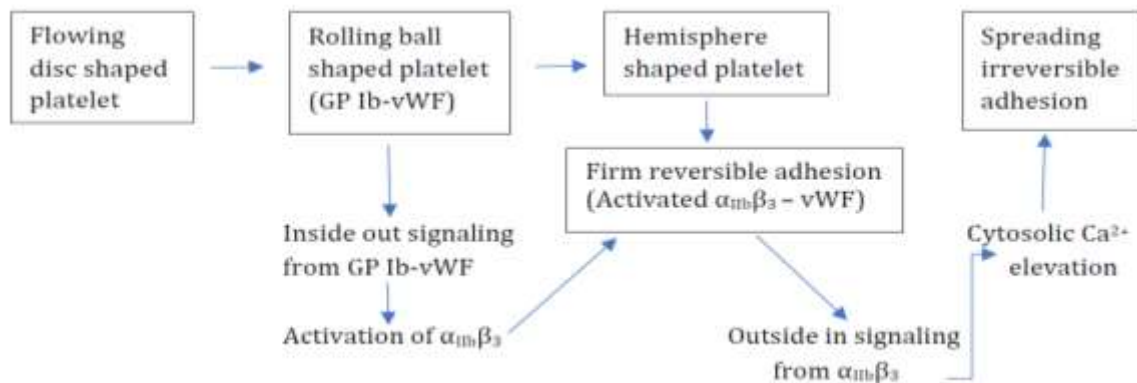
Aggregation

- Formation of hemostatic plug by interaction of platelets, vWF, collagen and glycoproteins

Platelet granules

Secretion of granules by activated platelets through their microcanalicular mechanism to the exterior.

Granules	Significance
α granules	Contains P selectin, platelet factor 4, TGF- β 1, PDGF, fibronectin, β -thrombomodulin, vWF, fibrinogen, factors 5 and 13
δ granules	Contains ADP or ATP, calcium and serotonin
γ granules	Contains lysosomes
λ granules	Involved in clot resorption during later stages of vessel repair

Morphological change of platelets**Aggregation**

Role in aggregation	Tethering, translocation	Platelet-platelet cohesion	Stabilization
Receptor interactions	GP Ib/V/IX - vWF	$\alpha_{IIb}\beta_3$ - fibronectin, vWF	$\alpha_{IIb}\beta_3$ - fibrinogen, fibronectin

Benefits of PRP

- Acts as a biological and natural healing cascade for the disease
- Increases the concentration of growth factor levels at the injury site
- Provides a provisional matrix or scaffold for healing
- Has anti-inflammatory & antimicrobial properties
- Processing and application patient side is simple and rapid
- Eliminates the risk of disease transmission
- Eliminates immunological concern of the disease

Families of platelet concentrates – Based on presence of leukocytes and fibrin architecture ^[4]

A. Pure Platelet Rich Plasma contains plasma with high concentrate of platelets, low density fibrin network without

leukocytes

- B. Leukocyte and Platelet Rich Plasma contains plasma with high concentrate of platelets and leukocytes, low density fibrin network without leukocytes
- C. Pure Platelet Rich Fibrin contains high concentration of platelets without leukocytes with high density fibrin network
- D. Leukocyte and Platelet Rich Fibrin contains high concentration of platelets with leukocytes with high density fibrin network

Mechanism of action of PRP

The binding of growth factor to target cell receptor induces a signal transduction mechanism which produces a biological response for chemotaxis, cell proliferation and osteoblastic

differentiation. The molecular basis of platelet rich plasma is due to increased HGF and TNF- α activity by disrupting NF- κ B-transactivating activity [5].

Uses of PRP in Orthopedics

- A. Ligament injuries – Strains and sprains of MCL and LCL injuries.
- B. Tendon injuries – Achilles tendinitis, Rotator cuff injuries, Quadriceps tendinitis & Patellar tendinitis
- C. Overuse syndromes – Medial epicondylitis, Lateral epicondylitis, Plantar fasciitis
- D. Muscle injuries – Tear of quadriceps, hamstrings, biceps, triceps and calves.
- E. Cartilage injuries – Osteoarthritis of hip, knee & shoulder, Periarthritis of shoulder, Patello-femoral chondrosis
- F. Bursitis – Olecranon bursitis, Supra patellar bursitis, Pre patellar bursitis, Infra patellar bursitis, Retrocalcaneal bursitis, Subacromial bursitis, Trochanteric bursitis
- G. Knee injuries – Anterior cruciate ligament (ACL) injuries and meniscal tears.
- H. Entrapment syndromes – Carpal tunnel syndrome
- I. Spinal injuries – Lumbar spinal disc pain, SI joint pain

Contraindications of Platelet Rich Plasma

- Patients consumed NSAIDs prior to 1 week of PRP therapy
- Patients consumed local corticosteroid infiltration within 1 month of PRP therapy
- Patients with haemoglobin < 7 gm/dL
- Patients with thrombocytopenia < 1,50,000/ μ L
- Patients with septicaemia, diabetes, rheumatological diseases
- Patients with seropositivity for HIV, HbsAg, HCV, syphilis
- Patients with local infection at the pathological site

Pre-procedural considerations

1. Absolute indication for PRP therapy should be figured out which should be correlated with clinical and radiological examination prior to treatment.
2. Patient education regarding pre- and post-procedural care
3. Informed and written consent to be taken prior to the initiation of procedure
4. Patient should not have taken analgesics 48 to 72 hours prior and local steroid infiltration within 4 weeks prior to PRP therapy

Autologous PRP preparation [6]

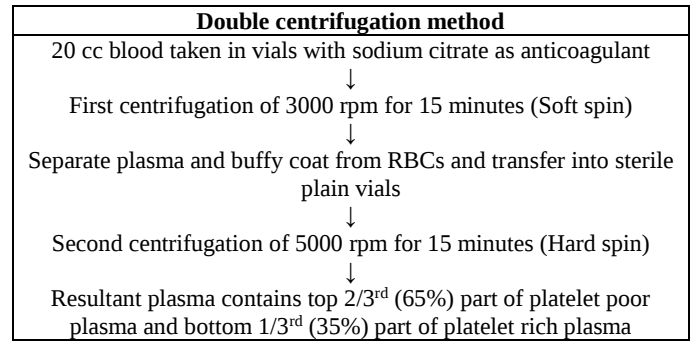
A) Withdrawal of blood from patient

- Using aseptic technique, 20 ml of venous blood is withdrawn for the given procedure and transferred to vials with contain acid citrate dextrose anticoagulant.
- Multi puncture of venous site leads to mechanical activation of platelets.
- Proper labelling of each vial should be performed.

B) Autologous PRP preparation

- A 20 cc venous blood will yield 3 – 4 cc of PRP depending on the baseline platelet count of an individual.
- PRP is prepared by a process known as differential centrifugation which is based on the acceleration force and the specific gravity.

Method of PRP preparation



- Activation of PRP
 - PRP can be activated exogenously by thrombin, CaCl₂ or trauma and endogenously by collagen,
 - Once PRP is activated, the fibrinogen – fibrin tetrameric complex forms and solidifies to form a fibrin clot which is also called as PRP gel.

PRP injection technique

- The patient should be placed in an appropriate position which is specific to a specific musculoskeletal disorder.
- With a proper sterile precautions, the pathological site is to be painted and draped with betadine.
- Before injecting PRP to the pathological site, 10% calcium chloride is added to the PRP in the ratio of 1:10.
- Once calcium chloride is added to PRP solution, without any further delay, under ultrasound guidance, the injection should be given at the point of maximum tenderness. If the process of injecting PRP is delayed after mixing calcium chloride, there are high chances of PRP to get activates which further forms a gel.
- Crepe bandage application is given with post-procedural advice.

Post injection events

Once PRP is activated with 10% of calcium chloride, a fibrinogen – fibrin tetrameric complex begins to form and solidify to form PRP gel. A tetrameric PRP gel contains platelets and growth factors. Activated PRP coagulates to form a gel which leads to degranulation of platelet granules (α , δ , γ and λ) within 10 minutes of injection [7].

The phases of activated PRP follows four phases namely

- a. Inflammatory phase is characterized by increased vascular permeability, initiation of angiogenesis, stimulation of tenocyte proliferation and initiation of type III collagen synthesis over injection site which lasts for 48 – 72 hours
- b. Proliferative phase is characterized by accumulation of fibroblast proliferation and neoangiogenesis which lasts from 1 to 6 weeks. During this phase, water content and glycosaminoglycan concentration remains high.
- c. Remodelling phase commences approximately after 6 weeks and lasts till 10 weeks with decreased cellularity and decreased collagen and glycosaminoglycan synthesis
- d. Maturation phase is characterized by synthesis of type I collagen which lasts from 10 weeks to 6 months. In this phase, the metabolism of tenocyte remains high.

If the patient recurs with symptoms, the next dose of PRP injection should be given with an interval of 3 weeks. The time duration of 3 weeks is provided for the initiation of fibroblast proliferation and neoangiogenesis.

Post procedural care

- Monitor for post procedural complication – Vasovagal attack
- Adequate immobilisation for 24 to 48 hours
- Counselling regarding post procedural activity and mobilization
- Post procedural pain must be combated with paracetamol or tramadol
- Avoid NSAIDs following the procedure for minimum of 2 weeks since it interacts with cyclooxygenase pathway

Follow-up

- Follow up examination of patients are generally done 4 weeks after the procedure to monitor pain, functional outcome and range of movements and to discuss the further course of disease and its outcome.
- Patient's response should be recorded using validated outcome measures.
- Complications following the procedure to be tracked out and recorded.
- Consideration for re-injection is an individualised approach which is based on functional status of the pathology.

Future prospects

Further research on the amount of growth factors to be injected, dosage and protocol are necessary to improve the longevity of platelet rich plasma and its usage to treat sports related musculoskeletal injuries ^[8].

Conclusion

Percutaneous therapy of platelet rich plasma with osteoinductive, osteoconductive and osteointegrative properties has become the treatment of choice for musculoskeletal disorders which improves the functional quality of life.

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