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PLATELET CONCENTRATES IN PERIODONTICS - A REVIEW

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ABSTRACT

Platelet concentrates (PCs; platelet-rich plasma and platelet-rich fibrin) are autologous bioactive substances that have found varied application in medical and dental fields, particularly in oral and maxillofacial surgery, periodontal plastic surgery, The rationale of these technologies is to extract all the elements from patient's own blood sample, which could be used to improve healing by promoting tissue regeneration by releasing the growth factors. PCs have evolved a long way since its introduction in 1954. PCs have been used successfully in periodontics and implant dentistry. However, the preparation protocol, processing time, transfer of concentrates, centrifugation temperature, vibration, etc., being not standardized are various factors for the mixed results reported in the literature. This review intends to discuss historical evolution of PCs, classification, mechanism, their preparation techniques, and their clinical aspect, recent advantages and applications.

INTRODUCTION

Platelets are anucleate cytoplasmic fragments derived from bone marrow megakaryocytes and measure 2–3 μm in diameter. Platelet concentrates collected from whole blood was first introduced over 20 years ago. The concept was developed with the aim of utilizing human blood proteins as a source of growth factors capable of supporting angiogenesis and tissue ingrowth based on the notion that blood supply is a prerequisite for tissue regeneration.

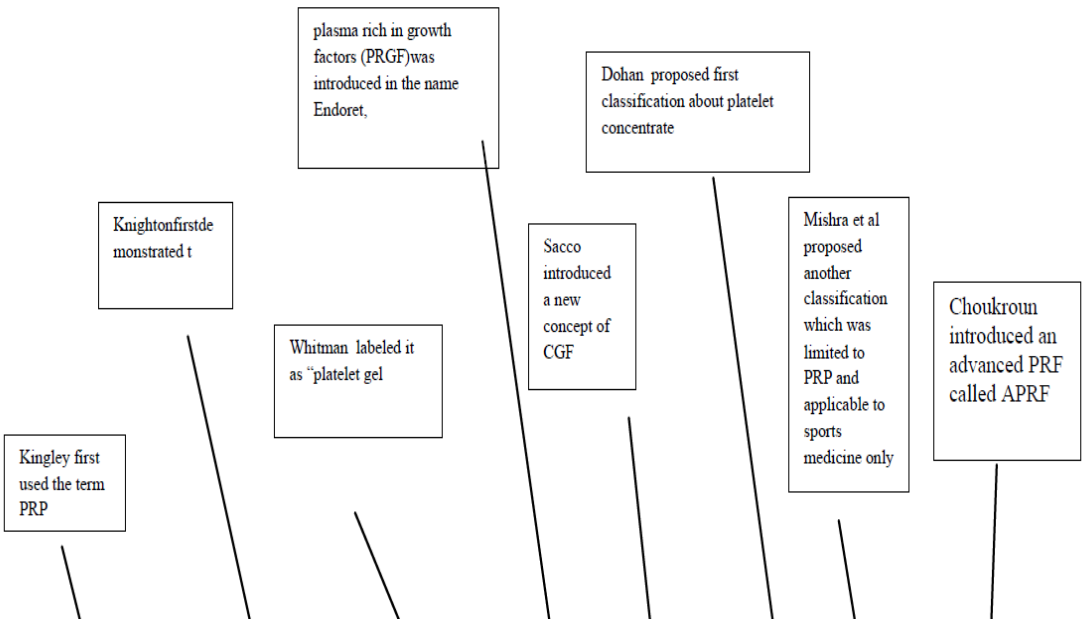
The pivotal goal in periodontal and maxillofacial tissue regeneration is to reconstruct these defects which led to the search of a biofuel. Focus has constantly been on devising a "wonder material" that is most effective in its regenerative potential.[1] Various platelet-derived products or platelet concentrates have been introduced that act as biological mediators aiding the healing response.

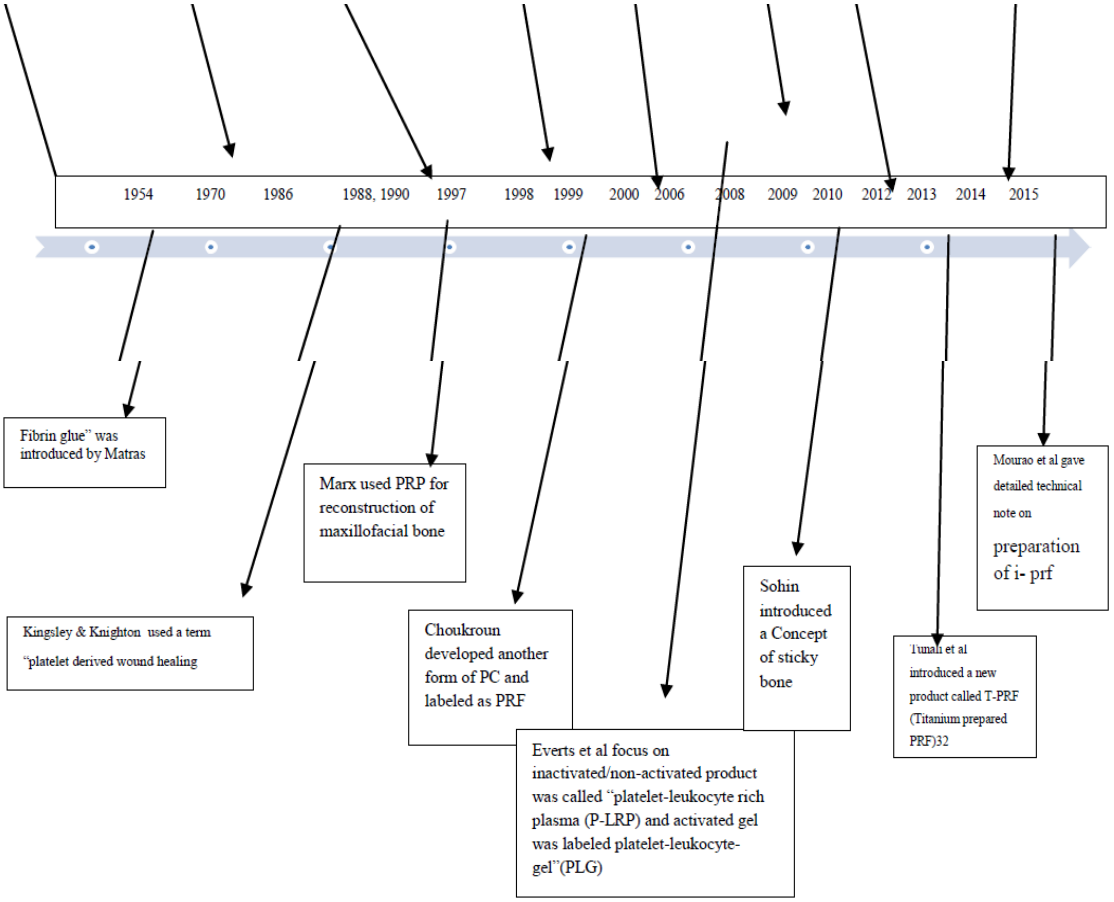
The world of medicine was acquainted with the regenerative potential of platelets in 1974. The platelet concentrates have been used for the improvement of reparation and regeneration of the soft and hard tissues after various periodontal surgical procedures.

Platelet concentrates are blood derivatives, prepared from the patient's own blood and containing autologous platelets growth factors and cytokines involved in the key processes of tissue regeneration, including cell proliferation and differentiation, extracellular matrix synthesis, chemotaxis and angiogenesis.

Platelets have also been shown to secrete a number of important growth factors including plateletderived growth factor (PDGF), vascular endothelial growth factor (VEGF), coagulation factors, adhesion molecules, cytokines/chemokines, and a variety of other angiogenic factors capable of stimulating the proliferation and activation of cells involved in the wound healing process including fibroblasts, neutrophils, macrophages, and mesenchymal stem cells (MSCs)

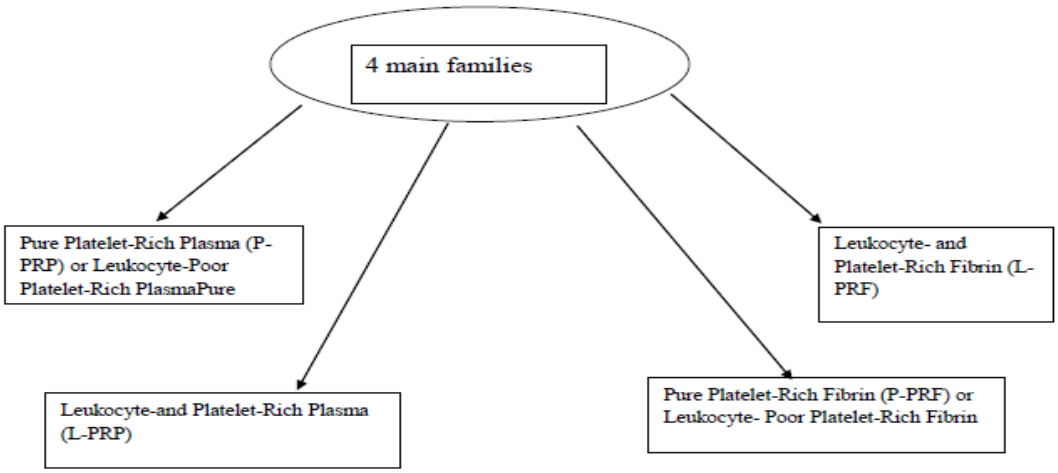
History: The use of platelet concentrates have dramatically increased in popularity over the past decade since the discovery of PRF. Despite this, it is important to understand that growth factors derived from blood had been used in medicine for over two decades.





Current general classification

DOHAN ET AL first classification was proposed in 2009 and is now widely cited as a milestone in the process of clarification of the terminology. This classification is actually very simple, and separated the products following at least 2 key parameters: the presence of a cell content (mostly leukocytes) and the fibrin architecture. This separation allowed to define 4 main families to regroup the products.



This classification system was largely cited, advocated, and validated by a multidisciplinary consensus conference published in 2012. The POSEIDO (Periodontology, Oral Surgery, Esthetic and Implant Dentistry Organization) hold it as its guidelines for all publications on the topic in 2013.

Current Poseido Classification System:The POSEIDO recommendations are based on the above mentioned classification of platelet concentrates for surgical use, and will serve as a basis for future evolutions of the terminology and recommendations for clinical use.

Platelet Concentrate Class and terminology	**Methods of production** (Generic name, detailed appellation when existing, company, city, country)
P-PRP (Pure Platelet Rich Plasma), Before activation (**P-PRP gel**, after activation)	• Cell separator PRP (experimental) • Vivostat PRF (Vivolution, Alleroed, Denmark)
	• PRGF/Endoret (Preparation or Plasma Rich in Growth • Factors, BTI BioTechnology Institute, Vitoria, Spain) • E-PRP (Eye Platelet-rich Plasma, experimental) • Nahita PRP (Nahita, Navarra Spain)
L-PRP (Leukocyte- and Platelet-Rich Plasma), before activation (**L-PRP gel**, after activation)	• PCCS PRP (Platelet Concentrate Collection System, 3I, USA) • SmartPReP PRP (MA, USA) • Magellan PRP (Magellan APS (Autologous PlateletSeparator), USA) • Angel PRP (Angel Whole Blood Processing System (Italy) • GPS PRP (Gravitational Platelet Separation System, IN, USA) • Friadent PRP (Friadent- Schütze, Vienna, Austria) • Curasan PRP (Curasan, Kleinostheim, Germany) • Regen PRP (Regen Laboratory, Mollens, Switzerland) • Plateltex PRP (Plateltex, Prague, Czech Republic) • Ace PRP (Surgical Supply and Surgical Science Systems, Brockton, MA, USA)
P-PRF (Pure Platelet Rich Fibrin) **L-PRF(Leukocyte- and Platelet-Rich Fibrin)**	Fibrinet PRFM (Cascade Medical, Wayne, NJ, USA) Intra-Spin L-PRF (Intra- Lock, Boca Raton, FL, USA)Titanium-prepared PRF (experimental)

Recent classification of PRP: Arun k Garg 2018

PRP L -PRP Liquid	1000-2200 rpm,8-12 min
PRP G -PRP gel	1000-1500 rpm , 5 min

PRP M – PRP membrane	1000-1500 rpm , 5 min
PRP E -PRP exudate	1000-1500 rpm , 5 min
PRP plug	1000-1500 rpm , 5 min
Gummy bone	3500 rpm ,2-4 min
PRP with heated proteins	1000-2200 rpm , 8-12 min

Platelet rich plasma: First Generation Platelet Concentrates

Platelet-rich plasma is a volume of autologous plasma that has a platelet concentration above baseline. Normal platelet counts in blood range between 150,000/µl and 350,000/µl and average about 200,000/µl. Because the scientific proof of bone and soft tissue healing enhancement has been shown using PRP with 1,000,000 platelets/µl, it is this concentration of platelets in a 5-ml volume of plasma which is the working definition of PRP today. Lesser concentrations cannot be relied upon to enhance wound healing, and greater concentrations have not yet been shown to further enhance wound healing.

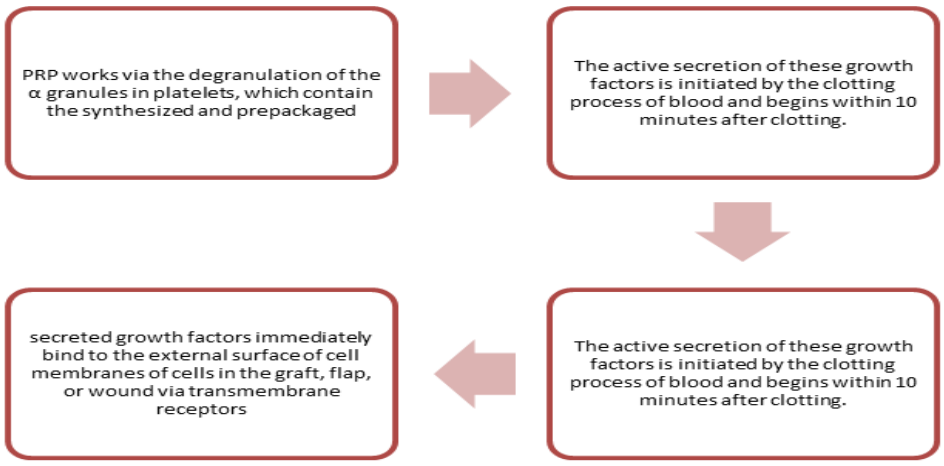
PRP and Growth factors

Because PRP is developed from autologous blood, it is inherently safe and is free from transmissible diseases such as HIV and hepatitis. Within PRP, the increased number of platelets delivers an increased number of growth factors to the surgical area.

The known growth factors in PRP are[117]

1. Platelet derived growth factor as: (PDGFaa), PDGFbb, PDGFab,
2. Transforming growth factor beta(TGF-b), TGF-b2
3. Vascular endothelial growth factor (VEGF), and
4. Epithelial growth factor (EGF).

Mechanism of action of PRP



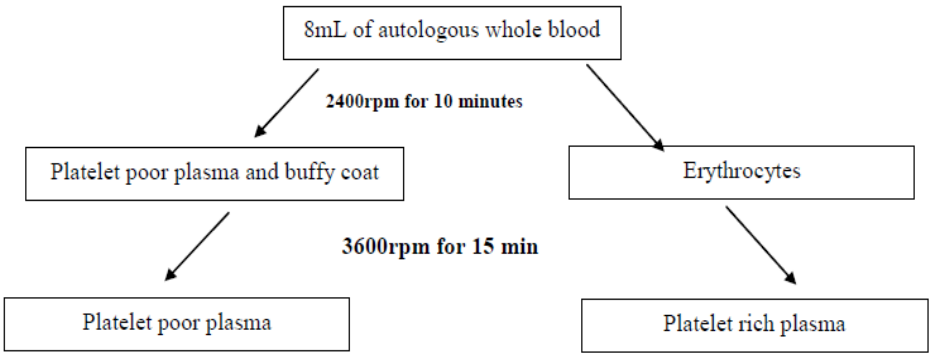
These transmembrane receptors in turn induce an activation of an endogenous internal signal protein, which causes the expression of (unlocks) a normal gene sequence of the cell such as cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc

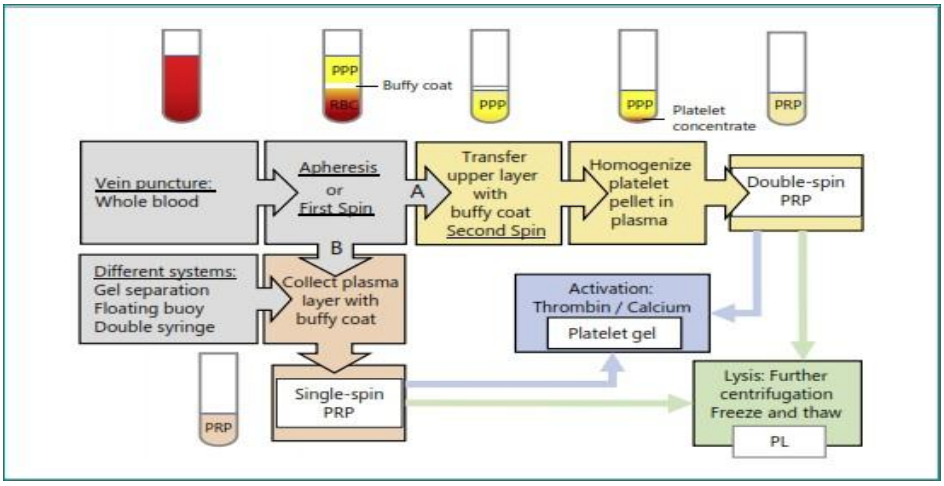
After the initial burst of PRP-related growth factors, the platelets synthesize and secrete additional growth factors for the remaining 7 days of their life span.

Therefore, the number of platelets in the blood clot within the graft, wound, or adherent to a flap sets the rate of wound healing. PRP merely increases this number[118].

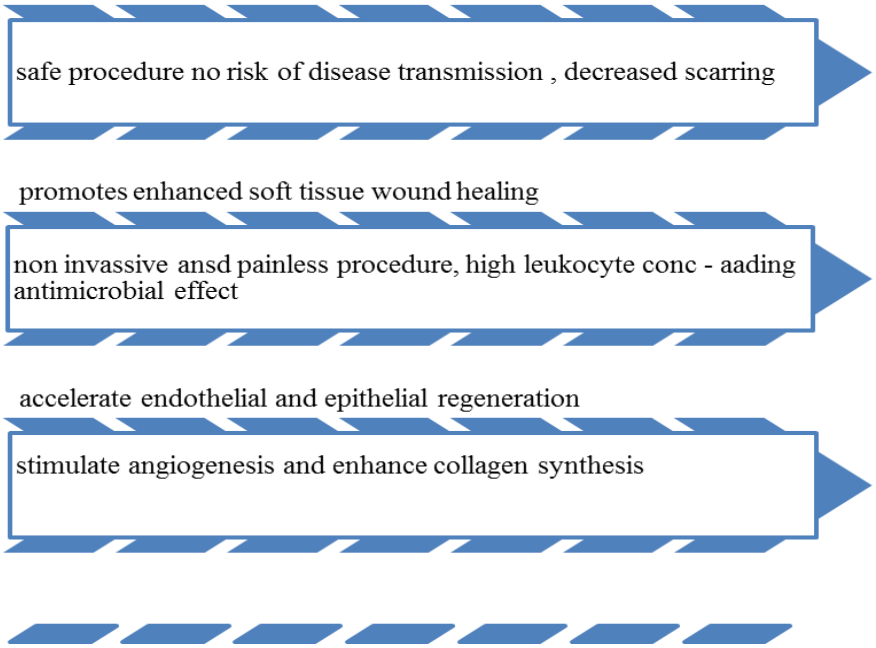
Processing PRP

Steps in the preparation of platelet-rich plasma





Advantage of PRP



Litrarature review

Authors	Year of publication	Number of patients	Treatment	Follow- up	Main results	Effect of PRP
Marx et al	1998	44	Intrabony defects in mandible	6mnth	Radiographically positive effects seen	strong
Jaske et al	2003	15	Intrabony defects	6mnth	Superior regenerative effects	Strong
radeep et al.	2009	20	Treatment of furcation defects	24	No complete closure of furcation defects	Weak
aini et al.	2011	20	Treatment of infrabony defects	12-24-36	Positive effect of PRP used with Other graft materials in infrabony defects	Moder ate
zdemir et al.	2012	14	Treatment of infrabony defects	24	Positive effect of PRP used with	Weak

Platelet rich fibrin: Second generation platelet concentrate

In the year 2000 PRF was first developed by choukroun and his co-workers for use in the field of oral and maxillofacial surgery.it contains platelets and growth factors in the form of

fibrin memebranes prepared from the patients own blood , free of anticoagulants or other artificial products.

PRF can be seen as an autologous biomaterial made of a fibrin matrix that contains the following:

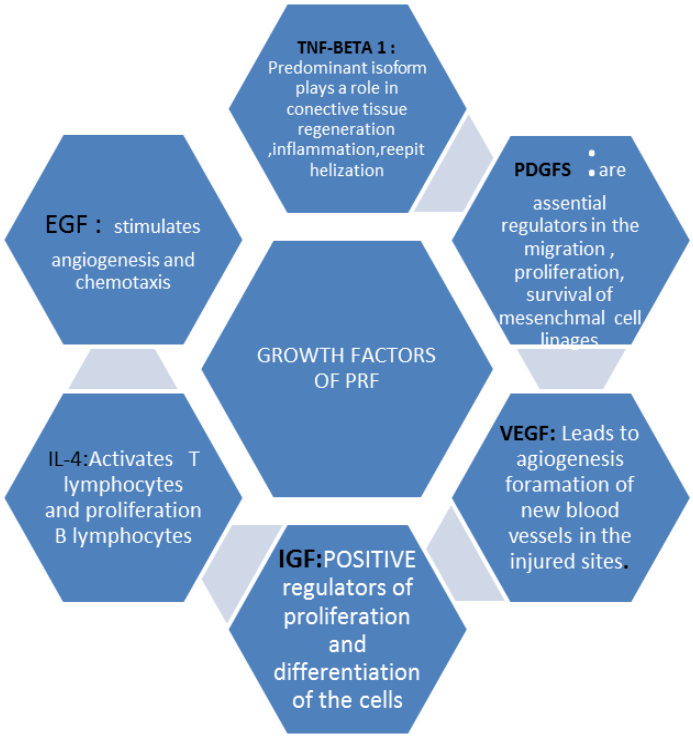
The highest concentration of platelets The highest concentration of growth factors, including

1. Platelet-derived growth factor (PDGF),
2. Vascular endothelial growth factor (VEGF),
3. Transforming growth factor (TGF) 〕

A representative concentration of fibrin, fibronectin, vitronectin, and thrombospondin 〕 An approximately 65% concentration of leukocytes

Growth factors

Its role and its functions



PRF is classified according to its leukocyte content as either L-PRF or P-PRF.

- L-PRF contains up to 90% of the platelets and at least 75% of the leukocytes present in the patient's blood.

Preparation of L-PRF

Blood samples (9–10 mL) are collected in sterile glass or plastic-coated tubes.

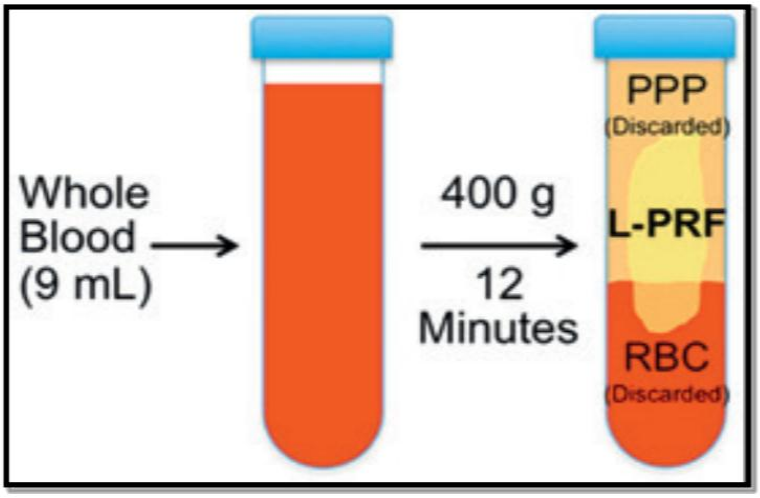
The tubes are placed in pairs and centrifuged at 400g RCF for 12 min using the Intraspin centrifuge (Intra-Lock International, Boca Raton, FL); 400g RCF is equivalent to 2700 rpm.

It is very important that the collection of blood and placement of the tubes in the centrifuge happen as rapidly as possible, before the spontaneous coagulation process occurs. Ideally, the tubes should be centrifuging within 60 seconds after the start of the venipuncture.

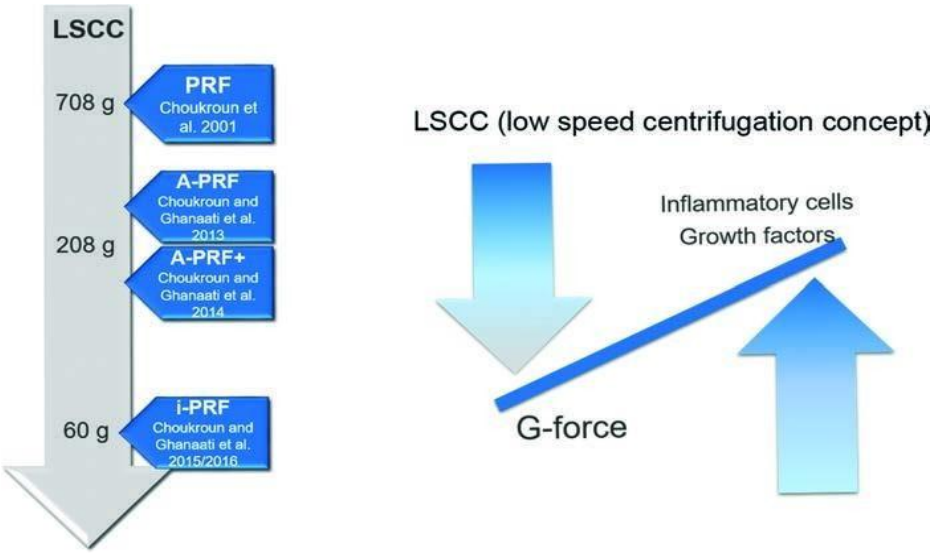
This often requires loading the centrifuge with tubes two by two or one by one. In the latter case, a tube filled with the same amount of glycerine or saline should be considered to balance the centrifugation

However, after centrifugation, due to the activation of autologous thrombin, it is converted to fibrin and a fibrin clot is created

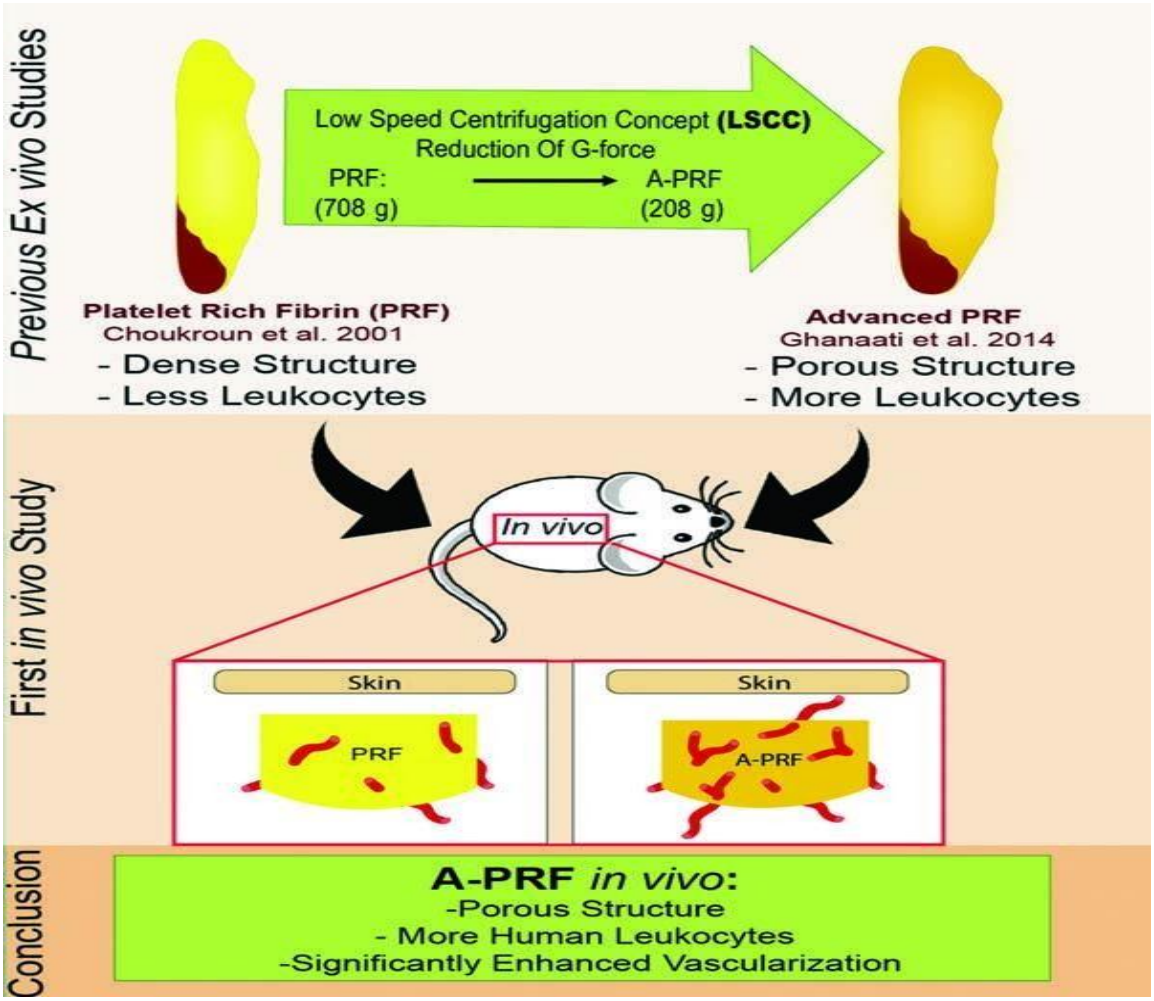
- After centrifugation, three distinct layers can be seen in the tube: red blood cells (RBCs) at the bottom of the tube, platelet-poor plasma (PPP) at the top of the tube, and the fibrin clot (containing most leukocytes and platelets) in the middle of the tube.



- The clot by itself contains a great amount of exudate, which is rich in growth factors.
- This exudate can be expressed by gentle compression of the clot (about 5 min) in order to obtain stronger L-PRF membranes.



Development of solid and injectable PRFs following the low-speed centrifugation concept (LSCC).



Advantages of prf over PRP

1. No biochemical handling of blood.
2. Simplified and cost effective
3. Use of thrombin and anticoagulant is not required
4. Healing is favorable
5. Helps in hemostasis
6. Supportive effect in immune response

Literature review

Author	Defect #	Number of cases	Healing Period	Treatment	Gain in CAL (mm)	p value
Sharma (2011)	Class II Furcations	36	9 months	OFD (open flap debridement) OFD +PRF	1.28 2.33	<0.001
Bajaj (2013)	Class II Furcations	72	9 months	OFD OFD +PRF	1.37 2.87	<0.05
Pradeep (2016)	Class II Furcations	105	9 months	1. OFD + placebo gel OFD + HA + PRF	1.82 3.31	<0.05 between all groups

Use of PRF for periodontal regeneration

Another area of research rapidly evolving is the use of PRF for periodontal regeneration of either intrabony or furcation defects.

Since PRF can be utilized as a safe, natural method to repair tissues at low-cost, many investigators and clinicians in private office have attempted to use PRF for the regeneration of periodontal defects.

Many randomized clinical trials are now available comparing PRF to open flap debridement alone or to other gold standards such as enamel matrix derivative (EMD).

These reports have shown significant improvements in periodontal pocket depth reduction as well as clinical attachment level gains following regenerative periodontal therapy with PRF.

Similar positive results have also been obtained for the treatment of furcation class II involvement. The collected clinical trials now demonstrate that using PRF alone or combined with other biomaterials such as bone grafts leads to statistically superior results when compared to open flap debridement alone or bone grafting material alone.

Recent advances in platelet concentrates

Platelets has been used extensively in medical and dental field since 1950s.

Concentrated growth factors

Theis concept was introduced by **Sacco in 2006**.

A special centrifugation machine (MEDIFUGE) is used. The process is similar to PRP but with different centrifugation speed. This newer technology allows it to separate a fibrin denser which is much denser, larger and richer in growth factore.

Preparation protocol sequence:
30sec acceleration
2min at 2700rpm/735g,
4min at 2400rpm/580g
4min at 2700rpm/735g
3min at 3000rpm/905g
36sec deceleration and stop

Titanium prepared platelets rich fibrin: T -PRF

T-PRF was introduced by **Tunali et al in 2013**

During the conventional PRP preparation procedure, researchers have pointed out that the possible health hazards caused by small particles which are small enough for a fraction to remain suspended colloidal in the buffy coat, fibrin and platelet poor layers of plasma.

These particles might enter in the patients body when the product is used for T-PRF is a newer method of preparation of platelets conc which is based on the hypothesis that titanium tubes mey be more effective at activating platelets than the glass tubes used in Chouckrouns method.

Advanced PRF (A-PRF)

Introduced by **Choukroun in 2014**. It has a good source of VEGF and Bone morphogenic proteins.

An attempt to incorporate the monocytes within PRF.as compared to the standard centrifugation protocol (2700 rpm,12 min)for the preparation of standard PRF, the centrifugation protocol for obtaining A -PRF is changed (1500rpm, 14min).

In the lower concentrated protocol, the presence of the macrophages was improved in the PRF. Because of these reason it is called A-PRF from the new protocol.

Advanced PRF (A-PRF) [+]

In the newer low speed concept, newer form of PRF have been described. in A-PRF +, the centrifugation protocol was changed to 1300rpm for 8min. A-PRF + demonstrated significantly higher total growth factor release compared with A-PRF and L-PRF.

Injectable –PRF (i-PRF)

The injectable fom of PRF is obtained by centrifugation of whole blood at 700rpm for 3-4min. When the particulate bone graft is added to i-PRF, the result is the formulation of a well agglutinated red coloured Sticky bone.

Centrifugation protocols

Original choukrouns PRF protocol (standard protocol)-3000 rpm/10min
Dohan ehrenfests group leukocyte and L-PRF- 2700rpm/12min
Choukroun adanced PRF enriched with leukocytes-1500rpm / 14 min
Choukroun i-PRF (solution /gel)- 700rpm/8min
Titanium PRF -2800rpm /12 min

CONCLUSION

PRF is increasingly being investigated and used by clinicians worldwide as an adjunct to autologous biomaterial to promote bone and soft tissue healing and regeneration.

It has also grabbed the attention because of its ease of availability from patients own blood.

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