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Injectable Platelet Rich Fibrin (i-PRF): A Gem in Dentistry

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ABSTRACT

Platelet-rich fibrin is the most innovative & commonly applied platelet concentrate in dentistry. Several modifications come across but injectable platelet-rich fibrin (i-PRF) showed unique properties. The objective of all this innovation is to find out all the components from the autologous blood to elucidate healing & application in tissue engineering. These i-PRF has achieved predictable and effective results. The main difference of i-PRF from solid PRF is the lower speed and time in centrifugation for i-PRF. i-PRF is the liquid variety of PRF which may accelerate the wound-healing processes with increased vascularization. The benefits of i-PRF show slow and sustained release of growth factors, by releasing the expression of transforming growth factor-β and collagen-1 mRNA along with cells migration. The use of platelet aggregates in injectable form is commonly used in orthopaedics and plastic surgeries. Because it is autogenous, it decreases the chances of adverse reactions to the implanted material as compared to other ways of grafting which facilitate better option in regenerative procedures. It has been observed that i-PRF found to be effective in periodontal wound healing and bone regeneration. This review article focuses on the current status of i-PRF formulation advantages and uses in regenerative surgery along with the healing process.

Key Words: Injectable Platelet-rich fibrin, i-PRF, Platelet-rich fibrin, Platelet concentrate

INTRODUCTION

Autologous blood concentrates show advancement in carrying higher concentrations of polypeptide growth factors to periodontal wounds. Amongst various platelet concentrates, platelet-rich fibrin (PRF) is 2nd generation preparations that were formerly described by Choukroun et al (2001).[1] The idea of PRF ushered in an era of the completely autologous form of platelet concentrates with no addition of bovine thrombin or anticoagulants. It is prepared by manipulation of patients own blood without any other additives.[2,3]

PRF is a surgical biologic preservative prepared from manipulating autologous blood.[4,5] It has one of the most extensively used platelets concentrates in dentistry which has unique formation. It played a role in carrying cells for the application of tissue regeneration. PRF used in plastic surgeries,[6,7] oral and maxillofacial surgeries [8] and implant [9] has observed efficient and effective concerning bone regeneration. The branch of periodontal therapy has currently explored the enormous benefits of PRF for the treatment of various types of periodontal defects.[10-13] Therefore, an attempt has been made to provide update literature on present status in regeneration and effectiveness of PRF. The development of platelet concentrates finds its origin in the concept of fibrin adhesives (**Table 1**).[14-17]

The most recent development in the field of PRF includes injectable PRF. As compared to PRP, one drawback that limits the applications of PRF is that PRF is obtained as a gel form it is not conducive to be injected. Recently, such an injectable or liquid variety of PRF has been developed.[18-22] It has uniqueness in the regeneration of human tissues. It has advancement through injecting patients autologous PRF in affected areas of soft tissue, mucous membrane or skin.[23-26]

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Table 1: Outlines the various evolution of Platelet concentrates

Nomenclature	Experimental outcome	Author & year
Platelet-rich plasma (PRP)	First experiments concerning blood Coagulation	Kingsley 1954 [14]
Fibrin glue	Observed better outcomes in the healing of wounds seen in rat models	Matras 1970 [15]
Platelet-fibrinogen-thrombin mixtures	many research works suggested an enhanced concept for using blood extracts	Rosenthal AR 1978 [16]
Platelet-derived wound healing factors	suggested that platelet concentrate effectively enhance healing	Knighton 1986 [17]
Platelet-derived wound healing formula (PDWHF)	used a slightly different term "PDWHF"	Knighton 1988 [18]
Platelet gel	produce end-product PRP but found in a gel consistency	Whitman 1997 [19]
PRF	developed in France and named due to the strong fibrin gel while polymerization	Choukroun 2000 [20]
Platelet Rich Gel	considered as an activated fibrin matrix rich in leukocytes, platelets & active molecule	Bielecki T 2006[21]; Bielecka A 2007 [22] Bielecka A 2009[23]
Concentrated growth factors (CGF)	introduced a new concept of CGF and used to separate the cells	Sacco 2006 [24]
Platelet-leukocyte rich plasma- inactivated leukocyte component of the platelet concentrate Platelet-leukocyte-gel- activated component		Everts 2008 [25,26]
Pure platelet-rich plasma (P-PRP) or Leukocyte-poor platelet-rich plasma (LP-PRP), (Leucocyte)L-PRP, (Pure)P-PRF, (Leucocyte) L-PRF classified as platelet concentrate based on cell content (primarily leukocytes) & fibrin structure.		Dohan Ehrenfest 2009 [27]
Sticky bone- It is an autologous fibrin glue with a combination of bone graft		Sohn 2010 [28]
PRP- This classification of PRP only applicable for sports medicine in which "solution" means non-activated PRP and "gel" considered as activated PRP Type 1(L-PRP solution), Type 2(L-PRP gel), Type 3(P-PRP solution), Type 4 (P-PRP gel)		Mishra 2012 [29]
Titanium prepared PRF- suggested new autogenous product with superior fibrin network		Tunali 2013 [30]
Advanced PRF- suggested holding more monocytes		Choukroun 2014 [31]
Injectable- PRF	The detailed technical note on preparation of i-PRF which forms the orange color fluid in injectable form	Mourão 2015 [32]

PREPARATION PROTOCOL OF i -PRF

A) According to Mourao et al [32]

Collect 9 ml of autologous blood in a test tube without any added preservative. Then centrifuged it for 2 min at 3300 rpm which forms the orange color fluid into the tube known as the I-PRF

B) According to Miron RJ et al. [34]

Collect autologous blood into plastic tubes without any added anticoagulants. Then centrifuged it for 3 minutes at 700 rpm. Use of plastic tubes has a hydrophobic surface which does not activate the coagulation process effectively. Hence, all the clotting factors & platelets of blood required for the formation of platelet concentrate reach the upper zone of the tube under the centrifugation force in the first 2-4 minutes. These separated plasma and platelets together situated at the upper layer in light yellow color used in injectable form.

C) According to Al-Maawi et al. 2019 [35]

Collected blood in the test tube was immediately kept in the centrifugation machine at 600 rpm, 44 × g for 8 min as per

low-speed centrifugation concept. After the centrifugation process, i-PRF formed of yellow orange-colored at the upper zone & other blood constituents at the lower zone.

D) Castro et al 2019, Cortellini et al 2018 [36,37] in their study modified the original protocol of injectable PRF. Collected blood-filled test tubes were kept in centrifugation machine for 2,700 rpm/ 3 min/ 408g.

E) According to Miron et al 2019 [38]

Horizontal centrifugation method was carried out for the preparation of i-PRF at 200g for 8 min. This produces a higher concentration of leukocytes 10.92 × 109 cells/L (178% original values) and platelets.

PROPERTIES OF i -PRF

1. i-PRF has been observed higher release of growth factor at the end of ten days such as Platelet-derived growth factor (PDGF) like PDGF-AA, PDGF-AB, Epidermal growth factor (EGF) and Insulin-like growth factor-1 (IGF-1) as compared to PRP
2. PRP and i-PRF demonstrated similar tissue compatibility
3. i-PRF demonstrated higher cellular migration.
4. Also, in cell culture, i-PRF induced significantly m-RNA expression of transforming growth factor (TGF-β) and collagen-1 at 7 days. This preliminary data hints that i-PRF may have comparative or slightly superior biologic properties as compared to that of PRP.
5. i-PRF is fibronectin which is an extracellular glycoprotein with a high molecular weight (approximately 440 kDa). Application of fibronectin to root surfaces improves cellular proliferation from the periodontal ligament towards the supracrestal parts.
6. The higher antimicrobial activity with I-PRF in case of Pg could be purely due to the higher concentration of platelets and other blood cells such as leukocytes in I-PRF as compared to the other platelet concentrates. This can be explained by Ghanaati et al. [39] concept of ' low-speed ' for blood centrifugation. He observed that low centrifugation speed contains a higher amount of cells with leukocytes before the fibrin clot development.
7. i-PRF has the bonding characteristics with the bone graft which permits proper adaptation of the defect area

USES OF i -PRF

i-PRF is being studied for its regenerative potential and release of growth factors along with Anti- Bacterial activity against Porphyromonas gingivalis (Pg) and Aggregatibacter actinomycetemcomitans.[40,41] i-PRF using microneedle can be effective for increasing gingival thickness [42] which elucidates through neoangiogenesis, neocollagenesis and better wound-healing. The application of i-PRF may be improved the success of periodontal therapy in individuals with thin gingival phenotypes, gingival recession defect,[43] infrabony defects and furcation defect. The possibility of bonding of i-PRF with bone grafts provides an alternative to PRP as a platelet aggregate for bone regeneration. This enhances the bone quality and used effectively in grafting Dental Implants.[44] The use of i-PRF in local drug delivery is an easy and convenient way due to its liquid or polymerized form and also applied as root surface bio-modification on root coverage.[45]

ADVANTAGES

1. It is in injectable form.
2. Can be used alone or in a combined form with various biomaterials.
3. The capacity of a high amount of regenerative cells with the release of more growth factors.
4. Formed a small fibrin clot with that worked as a dynamic gel.
5. Additive role in releasing growth factors for about 10 days.
6. It decreases the probability of adverse reaction

APPLICATION IN PERIODONTAL THERAPY

Wang et al. 2017[46] evaluated osteoblast behaviour by use of injectable PRF as compared to traditional PRP. The authors observed that PRP promoted 2 times more osteoblastic cells migration than control. Injectable PRF showed 3 times migration than control tissue culture plastic. The authors found that i-PRF have a significant increase in multiplication rate at 3- 5 days in comparison with PRP. They stated that the use of i-PRF showed more predictable results. **According to Wang et al.**[47] i-PRF can induce higher cell migration. Injectable PRF showed higher messenger RNA levels of PDGF, TGF-β, type I collagen and fibronectin than PRP. The authors concluded that i-PRF found to be an effective role & can be formulated without any anticoagulants.

Karde P et al. 2017[40] assessed the antimicrobial characteristics and platelet count of i-PRF as compared to other PRF, PRP and whole blood. Collection of blood samples were carried from chronic generalized marginal gingivitis individuals. Further antimicrobial activity against oral bacteria was investigated on blood agar using disc diffusion method to evaluate the inhibitory effects. The authors observed that i-PRF has a significant role in the inhibition of oral bacteria growth as compared to other platelet concentrates.

Varela et al. 2018[48] observed that i-PRF can induce higher cell migration and expressed TGF-β, PDGF, and type I collagen which stimulates the differentiation of osteoblasts and deposits mineral matrix.

Thanasrisuebwong et al. 2019[49] investigated the physical and biological characteristics of i-PRF preparation.

Collection of yellow i-PRF and red i-PRF fractionation was carried out from the upper yellow zone and both zone (yellow and red zone of the buffy coat) respectively. The authors concluded that red i-PRF showed more efficient biological characteristics & released growth factors in 7,14 day. Also, the yellow i-PRF found to be more viscoelastic characteristics.

Kour P et al. 2019[41] evaluated and compared the bactericidal effect of PRP, PRF & Injectable-PRF against Porphyromonas gingivalis (Pg) and Aggregatibacter actinomycetemcomitans (Aa). They stated that PRP and I-PRF have more efficient in bactericidal activity in comparison with PRF. Authors also concluded that the use of autologous i-PRF may act as an adjunct during the healing process and regeneration.

Izol et al.[45] investigated the outcome of i-PRF on root coverage of free gingival graft surgery. 40 subjects were treated with FGG in the control group and FGG with i-PRF used in the test group as a root modifier in cases of gingival recession. They achieved a positive effect on the closure of the root surface.

Fotani et al.[42] assessed the role of i-PRF in thin gingival tissue. 46 subjects were included & i-PRF application done with microneedle at baseline, 1 week and 2 weeks. The authors stated that the use of i-PRF through microneedle is less invasive and achieved better results in increasing gingival thickness.

Turer O et al.[43] studies investigated the combined effect of SCTG with i-PRF and SCTG alone in a coronally positioned flap procedure for the treatment of root coverage. The authors observed that the combined effect of SCTG and i-PRF achieved more amount of keratinized width and showed predictable results in reduced gingival recession.

Ozsagir et al. 2020[50] evaluated the efficacy of injectable platelet-rich fibrin alone and in combination with microneedling (MN) on gingival thickness (GT) and keratinized tissue width (KTW) in patients with thin biotype. They stated that microneedling has a beneficial result on the augmentation of Gingival thickness.

DISCUSSION

Over the last decade, the use of autologous blood concentrates has gained importance in the medical and dental areas. Blood concentrates are the carriers of growth factors which are used to enhance wound healing in the bone and soft tissue. Remarkable evolution in platelet concentrates has been since from the late 1990s in the last century.

The first generation incorporates the PRP which was developed to combine the fibrins sealant properties with growth factor effects of platelets. However, Lack of uniformity in PRP preparation protocol as different platelet concentrations have different storage time, the release of growth factors for a shorter period, may produce coagulopathies and rare bleeding episodes. This limits PRP's clinical application which calls for the alternative, clinically feasible strategies.

PRF is one such platelet concentrate which requires one spin and does not use anticoagulants for its procurement. The branch of periodontal therapy has currently explored the vast benefits of PRF for the treatment of various types of periodontal defects. The clinical benefit of PRF depends on the time interval between the speed of handling between blood collection and centrifugation process. As compared to PRP, one drawback that limits the applications of PRF is that PRF is obtained as a gel form which is not conducive to be injected.

Interestingly, over the past decade since PRF was developed and many clinicians now point to the potential use of a liquid version of PRF. One of the latest developments in the PRF technology is the production of injectable PRF (i-PRF). Liquid PRF, which was prepared according to the low speed of centrifugation, is a concentrate of platelets, leukocytes, and their growth factors in a liquid fibrinogen based matrix.[39]

Depending on the blood collection tube and the centrifugation protocol, it is possible to generate either a Solid or a liquid PRF matrix without anticoagulants. In terms of Solid PRF, platelets interact with the glass surface of the tube and activate their coagulation during the centrifugation procedure.[39] The liquid PRF is generated using a blood collection tube with a plastic surface that enables the generation of a liquid PRF matrix without the use of external anticoagulants. At room temperature, the resultant liquid PRF preserves its liquid condition for approximately 15 to 30 min and forms a fibrin clot thereafter.[51]

A small syringe with an 18G hypodermic needle is used for the collection of i-PRF.[52] The harvesting technique of i-PRF after centrifugation process has been described as the amount of the upper layer harvested can vary among individuals and the position of needle tips during harvesting can also be varied based on different clinical practice.

i-PRF is a new alternative to the platelet aggregate to different areas of dentistry enabling experts to further research this product which qualifies it as a viable option in regenerative procedures.

CONCLUSION

This innovative advancement in the field of PRF such as i-PRF has paved way for the usefulness in the applications of platelet concentrates. It influences osteoblastic behaviour with a tremendous release of growth factors alone or in combination with biomaterials. Due to the presence of growth

factors and platelets it has the efficiency to convert osteoconductive graft into osteopromotive. Thus i-PRF has been demonstrated as modernized tools and achieved predictable outcomes in the dentistry field. But there should be more research required to determine the cell differentiation activity of components of i-PRF. Precise protocol for optimal preparation & its application on mucogingival surgeries is yet to be determined.

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