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Titanium Platelet Rich Fibrin(T-PRF): A Superior Choice Over Conventional Platelet Concentrates.

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Abstract :

INTRODUCTION- Titanium-Prepared Platelet-Rich Fibrin (T-PRF) represents an advanced modality in the field of regenerative medicine, leveraging the synergistic effects of titanium and autologous platelet concentrates to enhance tissue healing and regeneration.

AIM-This review aims to provide a detailed examination of T-PRF, focusing on its preparation, properties, and clinical applications.

SIGNIFICANCE OF T-PRF- The clinical use of glass coated plastic tubes with silica activators for the preparation of platelet concentrates may cause potential health concerns because of possible cytotoxicity of silica. Hence instead of glass coated tubes, the use of medical-grade IV titanium tubes for PRF preparation is relevant and safe. The development of third generation concentrate i.e. T-PRF (Tunali et al 2014) is based on the hypothesis that titanium tubes might be more effective in activating platelets than the glass tubes used in Choukroun's platelet-rich fibrin (PRF) method. Titanium has one of the highest strength-to-weight ratios and corrosion resistance among metals offering improved hemocompatibility, platelet activation similar to silica, and the advantage of reusability after proper sterilization, while being durable. The incorporation of titanium is hypothesized to enhance the stability and release of growth factors thereby promoting superior regenerative outcomes compared to traditional PRF. Furthermore, it evaluates the clinical evidence supporting its use in various dental applications, such as periodontal therapy, bone grafting and soft tissue repair. Emerging studies indicate that T-PRF offers significant advantages in terms of biocompatibility, growth factor release, and mechanical properties.

CONCLUSION- T-PRF emerges as a promising tool in regenerative medicine, with the potential to enhance clinical outcomes through its unique preparation and biological properties.

Keywords **– T-PRF, Titanium, Platelet concentrates, L-PRF**

INTRODUCTION

Platelet concentrates in transfusion medicine were primarily employed to manage and prevent bleeding associated with severe thrombocytopenia, commonly resulting from conditions like bone marrow failure, acute leukemia, or extensive surgical procedures. These concentrates, traditionally referred to as platelet-rich plasma (PRP), typically contained around 0.5 x 10^{11} platelets per unit.[1]

In the 1970s, PRP initially found application as a surgical adhesive, serving as a "glue" during surgical procedures. Notably, PRP at that time closely resembled the modern-day fibrin glue.[2] In contemporary practice, fibrin glue is typically derived from platelet-poor plasma (PPP).[3] According to Lekovic et al, the blood was drawn from patient's antecubital vein and mixed with an anticoagulant and centrifuged to separate in 3 layers Platelet poor plasma (PPP), Platelet-rich plasma (PRP) and Red blood cell (RBC) base. This PRP was then mixed with autologous thrombin for use.[4]

In the year 1999, Anitua et al. developed Plasma rich in growth factors (PRGF).[5,6] According to Anitua and colleagues, PRGF (Plasma Rich in Growth Factors) stands out from other PRP (Platelet-Rich Plasma) preparations due to its purely autologous and biocompatible formulation. This is achieved through a single-step centrifugation process that uses sodium citrate as the anticoagulant and calcium chloride both as the platelet activator and coagulant.[7]

In the year 2000, Choukroun introduced Platelet- rich fibrin (PRF) as an advanced platelet concentrate.[8] PRF is characterized by a matrix of glycanic chains, cytokines and glycoproteins enclosed within a fibrin network.[8] Clinical experience confirms that PRF (Platelet-Rich Fibrin) can be regarded as a healing biomaterial, possessing all the essential parameters for optimal healing. These include a fibrin matrix polymerized in a tetramolecular structure, the incorporation of platelets, leukocytes, cytokines, and the presence of circulating stem cells.[9] The PRF protocol includes blood sample collected in 10-mL dry glass/ glass coated plastic tubes without using an anticoagulant. These tubes are then immediately centrifuged at 3000 rpm (which corresponds to approximately 400g) for a duration of 10 minutes.[10]

Choukroun et al, have proposed theories and made further modifications to PRF to develop A-PRF (leukocyte-enriched, advanced type), i-PRF (injectable type), and CGF (Concentrated Growth Factor).[11,12,13] Based on the centrifugation devices used, further modifications of PRF were done to obtain H-PRF (horizontal PRF), C-PRF (Concentrated PRF) and Alb-PRF (Albumin PRF).[11,12,13]

EVOLUTION OF PLATELET CONCENTRATES OVER THE YEARS

YEAR	PLATELET CONCENTRATES	AUTHORS
1954	PRP (Platelet Rich Plasma)	Kingsley [14]
1970	Fibrin glue	Matras [15]
1975-1978	Platelet-fibrinogen-thrombin mixtures[16]	–
1979	Gelatin platelet-gel foam[17]	–
1986	Platelet-derived wound healing factors (PDWHF)	Knighton et al[18]
1988-1990	Platelet-derived wound healing formula (PDWHF)	Kingsley et al[14] & Knighton et al[19]
1997	Platelet gel	Whitman et al[20]
1998	PRP-Platelet Rich Plasma	Marx et al[21]
1999	PRGF- Plasma Rich in Growth Factor	Anitua[22]
2000	PRF-Platelet Rich Fibrin	Choukroun et al
2006	PRG-Platelet Rich Gel CGF-Concentrated Growth Factor	Bielecki et al[23] and Cieslik-Bielecki et al[24,25], Sacco[26]
2008	Platelet-leukocyte rich plasma (P- LRP) & platelet-leukocyte-gel" (PLG)	Everts et al [27,28]
2009	Pure platelet-rich plasma (P-PRP) – or Leukocyte-poor platelet rich plasma (LP-PRP) Leukocyte-and platelet-rich plasma (L-PRP) Pure PRF (P-PRF) -or leukocyte- Poor PRF(LP-PRF) Leukocyte- and platelet-rich fibrin (L-PRF).	Dohan Ehrenfest et al [1]
2010	Sticky bone	Sohn[29]

2012	L-PRP (Leukocyte-PRF) & P-PRF (Pure- PRF)	Mishra et al[30]
2014	A-PRF (Advanced-PRF)	Choukroun[11]
2014	T-PRF (Titanium-PRF)	Tunali et al[31]
2015	I-PRF (Injectable-PRF)	Mourão et al[32]
2017	A-PRF + (Advanced-PRF +)	Choukroun & Ghanaati[33]
2020	H-PRF (Horizontal PRF)	Feng et al[34]
2020	C-PRF (Concentrated PRF)	Miron et al[35]
2021	ALB-PRF (Albumin gel platelet-rich fibrin mixture)	Gheno et al[36]

Successful clinical outcomes have been reported with PRF but health hazard issues were raised by some physicians[37] as preparation of PRF takes place in a glass evacuated plastic collection tubes which releases silica particles which are dense enough to sediment with the red blood cells and small enough to remain suspended colloidally in the buffy coat, fibrin and platelet-poor layers of plasma.[31]

To overcome the health hazards caused due to silica particles Tunali et al in 2013 introduced Titanium-prepared platelet-rich fibrin (T-PRF) following a similar preparation method to that of leukocyte-platelet-rich fibrin (L-PRF) developed by Choukroun et al. in 2001.[31]

SIGNIFICANCE OF TITANIUM IN THE PREPARATION OF FIBRIN

The development of third generation concentrate i.e. T-PRF is based on the hypothesis that titanium tubes might be more effective in activating platelets than the glass tubes used in Choukroun's platelet-rich fibrin (PRF) method. Instead of glass tubes, medical-grade IV titanium tubes are utilized for T-PRF preparation, offering improved hemocompatibility, platelet activation similar to silica, and the advantage of reusability after proper sterilization, while being durable. Titanium has one of the highest strength-to-weight ratios and corrosion resistance among metals.[38] Due to its noncorrosive properties, titanium has excellent biocompatibility.[39] Also titanium has the ability to passivate itself by forming an adhesive oxide layer in vivo.[40] Titanium also displays a unique property of osseointegration, connecting both structurally and functionally with the underlying bone, and is commonly used in total joint replacements[41], dental implants, internal and external fixators, artificial heart valves, spinal fusion, and medical devices.[42]

T-PRF PREPARATION PROTOCOL

Blood samples are collected from the antecubital vein of the subject's arm, about 9 ml in total and are transferred into sterile medical grade IV Titanium tubes and immediately centrifuged at 2,800 rpm for 12 minutes to obtain a T-PRF clot.[40]

GROWTH FACTORS IN T-PRF

T-PRF demonstrates a higher percentage of platelets, monocytes, and lymphocytes compared to L-PRF, along with comparable amounts of progenitor cells.[43] T-PRF contains various growth factors such as transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF), which facilitate the healing process and contribute to achieving desired treatment outcomes.[43]

INVIVO STUDY ON T-PRF

Tunali et al (2014) studied the efficacy of T-PRF for wound healing in rabbit model. Blood samples from 6 rabbits were used to confirm the protocol for formation of T-PRF preparation. The T-PRF clots were converted into membranes and placed into the mucoperiosteal

flaps in the anterior mandibular regions and sutured. After 3,5,10,15 and 30 days, full thickness flap were raised and 7mm x 7mm samples were excised and stained with hematoxylin and eosin. The T-PRF clots were also subjected to scanning electron microscopic analysis to study its structure. The results found a mature fibrin network in T-PRF clots. Newly- forming connective tissue and islets of bony tissue were also observed in the T-PRF membrane. These results showed that T-PRF could induce the formation of new bone with new connective tissue in a rabbit model of wound healing within 30 days of treatment.[31]

LIGHT MICROSCOPIC ANALYSIS OF T-PRF

Tunali et al conducted light microscopic analysis for comparing T-PRF clot (Fig 1- A, B, C, D) and L-PRF clot (Fig 2-A, B, C, D) using H& E staining which revealed a well-organized homogeneous fibrin matrix with T-PRF clot. Also, fibrin border between cellular structures and the fibrin network of T-PRF appeared thicker and more prominent as compared to L-PRF clot.[40]

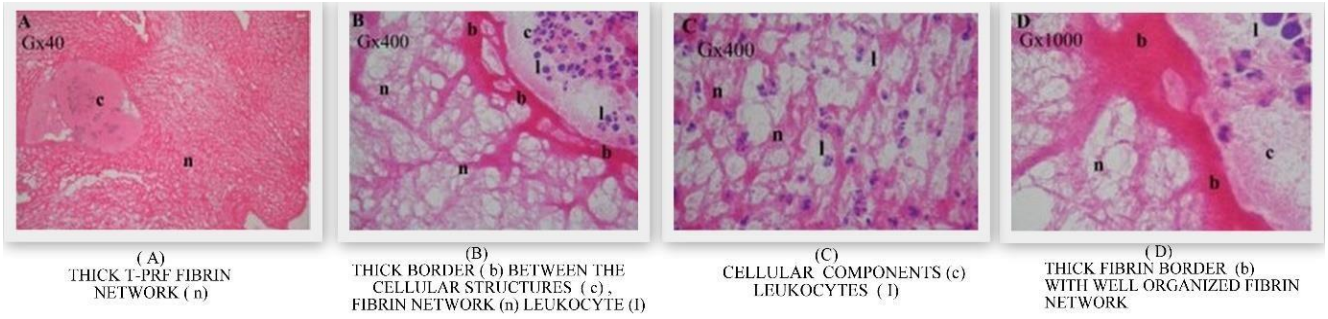

Fig 1. - Light microscopic analysis of T-PRF clot (Tunali et al) (2014)[40]

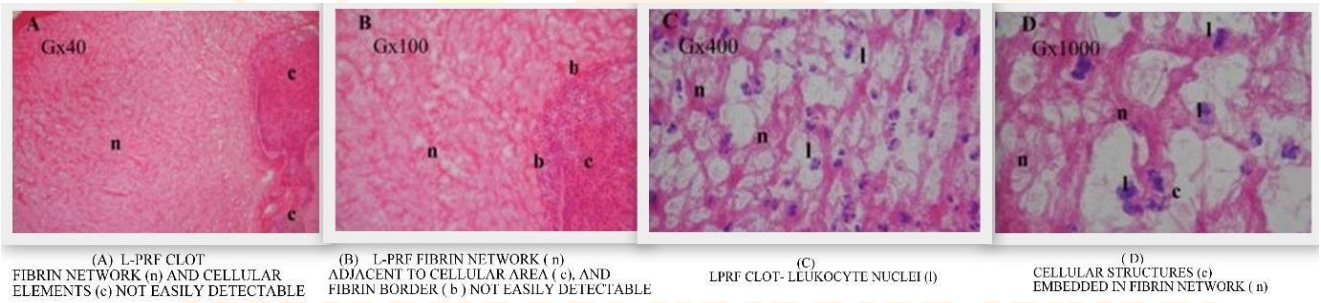

Fig 2-Light microscopic analysis of L-PRF clot (Tunali et al) (2014)[40]

FLUORESCENCE MICROSCOPIC ANALYSIS OF T-PRF

Immunofluorescent staining by Tunali et al[40] for comparing T-PRF (Fig 3) and L-PRF (Fig 4) clots revealed a mature and dense fibrin network with T-PRF clot. Also, the fibrin in the T-PRF samples appeared thicker and better organized.

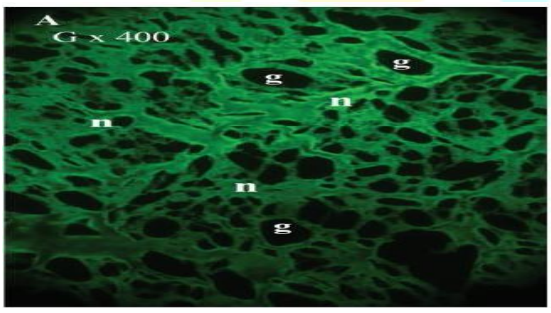

Fig-3 -Fluorescent microscopic analysis of T-PRF Clot

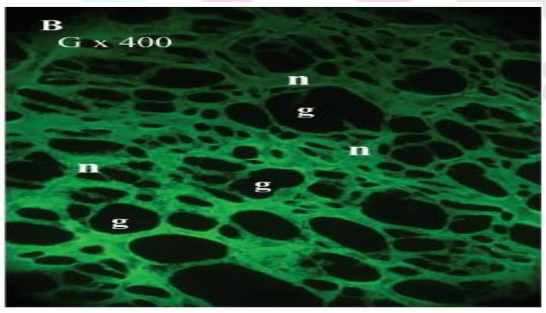

Fig-4-Fluorescent microscopic analysis of L-PRF Clot (Tunali et al) (2014)[40]

SCANNING ELECTRON MICROSCOPIC ANALYSIS OF T-PRF

Scanning electron microscopic studies undertaken by Tunali et al, revealed a well-organized matrix and advanced fibrin maturation with T-PRF clot as compared to L-PRF clot. The T-PRF clot mainly consisted of aggregated platelets and fibrin fibrils.[40](Fig 5)

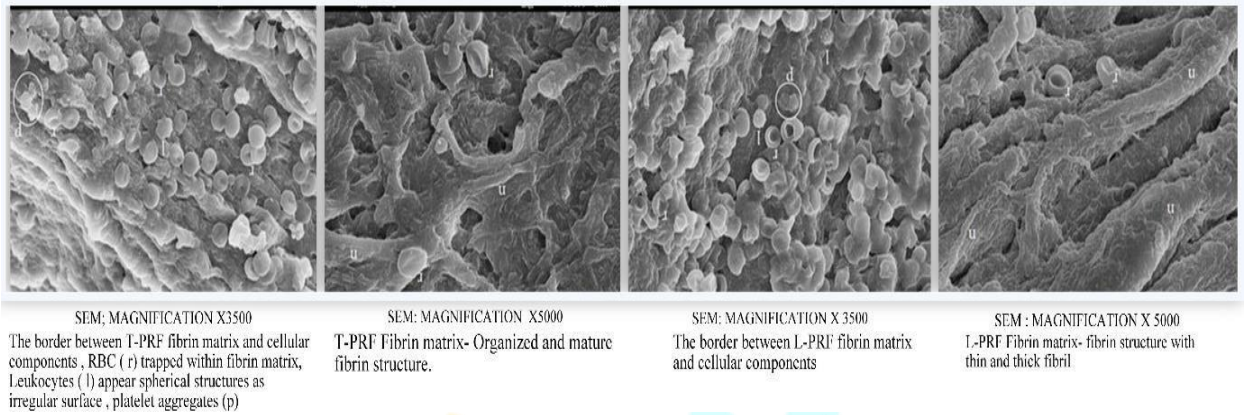

Fig 5- Scanning electron microscopic analysis of T-PRF & L-PRF clot (Tunali et al) (2014)[40]

HISTOMORPHOMETRIC EVALUATION OF T-PRF:

Histometric analysis of fluorescence microscopy conducted by Tunali et al images indicated that the T-PRF fibrin network covered a statistically significantly larger area compared to the L-PRF fibrin network.[40](Fig 6)

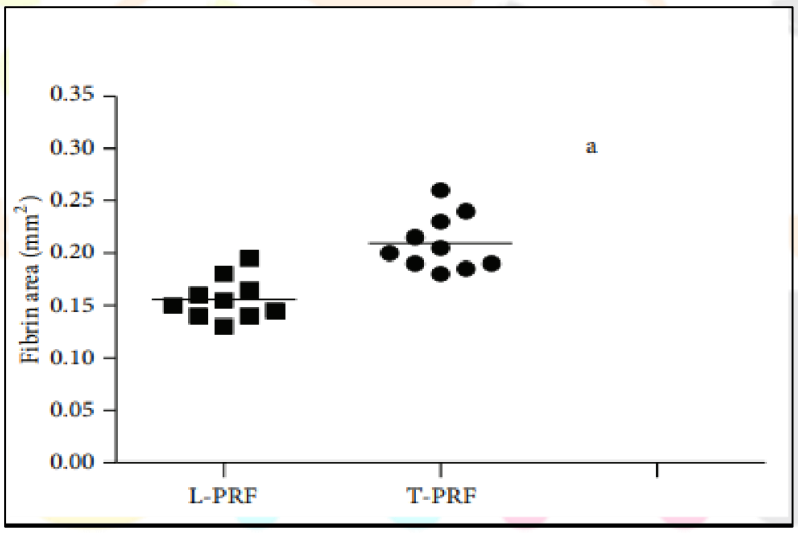

Fig 6 -Histomorphometry evaluation of T-PRF & L-PRF Clot (Tunali et al) (2014)[40]

TENSILE STRENGTH OF T-PRF-

Ravi S, Santhanakrishnan M. (2020) evaluated the mechanical properties of PRF membranes. Five samples were tested for the mechanical properties of PRF membranes. T-PRF showed the highest tensile strength (404.61 ± 5.92 MPa) and modulus of elasticity (151.9 ± 6.92 MPa), followed by A-PRF (362.565 ± 5.15 MPa, 122.51 ± 7.15 MPa), and L-PRF had the lowest values (290.076 ± 5.68 MPa, 98.01 ± 7.43 MPa). Statistical analysis confirmed significant differences between the groups.[43](Fig 7)

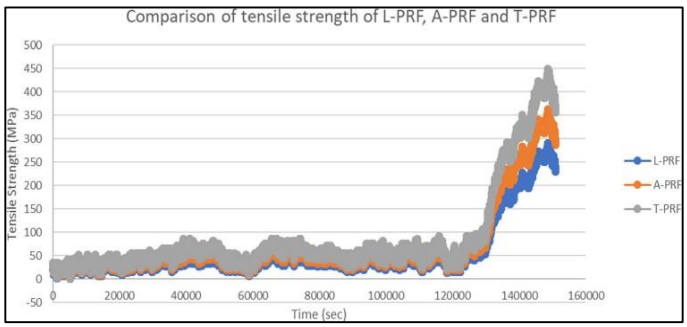

Fig 7-Histomorphometric evaluation of T-PRF & L-PRF Clot (Ravi S, Santhanakrishnan M) (2020)[43]

GROWTH FACTOR RELEASE PROFILE OF T-PRF

Ravi S, Santhanakrishnan M. (2020) analyzed PDGF-AA release using ELISA and found that T-PRF showed significantly higher levels initially (6060.4 pg/ml) compared to L-PRF (5721.3 pg/ml) and A-PRF (5935.3 pg/ml). T-PRF's PDGF-AA levels decreased after day 1, whereas A-PRF sustained its release over 10 days. No statistically significant differences were found between the groups at various time points, but trends indicated higher early release in T-PRF and sustained release in A-PRF.[43](Fig 8)

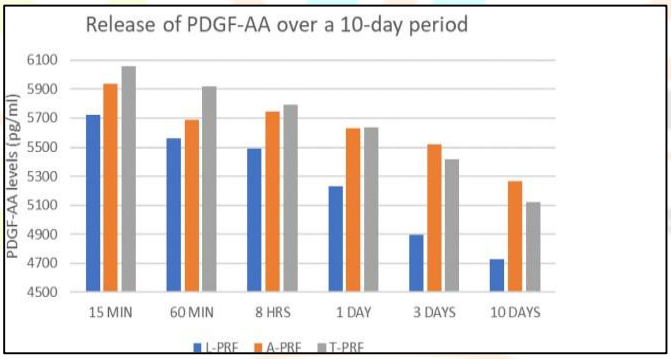

Fig 8-Growth factor release profile of L-PRF, A-PRF, T-PRF (Ravi S, Santhanakrishnan M) (2020)[43]

CHEMICAL DEGRADATION OF T-PRF -

Ravi S, Santhanakrishnan M. (2020) studied the chemical degradation of 3 types of PRF membrane. On placing the three types of PRF membranes in an orbital shaker, all three types degraded by up to 82%. L-PRF showed the highest degradation (85.75%), followed by A-PRF (84.18%), and T-PRF had the least (82.27%). T-PRF exhibited the best mechanical properties and the lowest degradation rate, while L-PRF had the highest degradation rate and the weakest mechanical properties.[43](Fig 9)

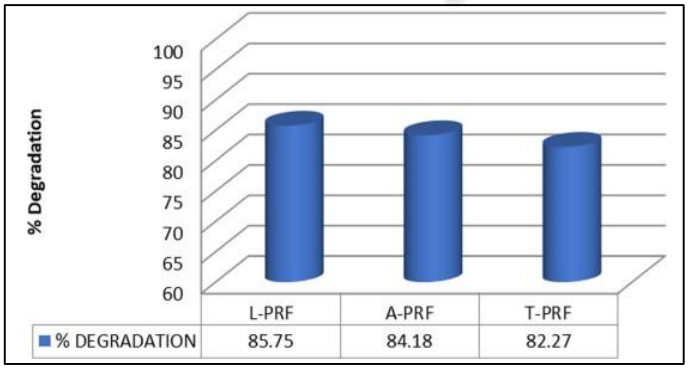

Fig 9-Chemical degradation of L-PRF, A-PRF, T-PRF (Ravi S, Santhanakrishnan M) (2020)[43]

APPLICATION OF T-PRF IN DIFFERENT PERIODONTAL PROCEDURES

1) In periodontal intrabony defects

Studies have utilized T-PRF with open flap debridement (OFD) in periodontal intrabony defects. The combined treatment significantly improved clinical parameters, growth factor levels, and the bone-filling rate compared to OFD alone, demonstrating superior outcomes in periodontal regeneration.[44,45,46,47,48]

2)In endo-perio lesions

T-PRF in combination with GTR has been utilized in endo-perio lesions. T-PRF showed similar effectiveness to GTR in treating intrabony defects with endo-perio lesions, with a significant difference in radiographic intrabony defects depth.[49]

3)In root coverage procedures

T-PRF has been also utilized in treating gingival recession. T-PRF significantly improved recession depth, width, and keratinized tissue width, and showed better gingival thickness and lower pain levels at various time points compared to PRF. T-PRF was found to be a safe and effective method for treating gingival recessions.[50]

4)In enhancing peri-implant tissue

Studies compared the effectiveness of titanium-prepared platelet-rich fibrin (T-PRF) and connective tissue graft (CTG) on peri-implant soft tissue thickness (STT), keratinized tissue width (KTW), and crestal bone level. Both T-PRF and CTG significantly increased KTW and STT, with the control group (CTG) showing a greater increase at certain levels. No crestal bone loss was observed, suggesting T-PRF as a viable alternative to CTG in enhancing peri-implant tissue health.[51]

5)Other applications

As T-PRF is similar to PRF membrane it can be used in furcation defects[52,53,54,55] after depigmentation in wound healing[56,57,58], as a scaffold for incorporation of drugs.[59,60]

CONCLUSION

Titanium-Platelet-Rich Fibrin (T-PRF) is a promising biomaterial in dentistry, offering significant benefits over traditional platelet concentrates due to its enhanced biocompatibility, structural integrity, and sustained release of growth factors. The use of titanium tubes in the preparation of T-PRF appears to enhance the quality and consistency of the fibrin matrix, providing a robust scaffold for cellular proliferation and differentiation.

Clinical studies have demonstrated its ability to accelerate healing, reduce postoperative complications, and enhance the integration of graft materials.

Overall, T-PRF represents a significant advancement in dental regenerative therapies, offering a reliable and effective option for enhancing patient care. As the field of dentistry continues to evolve, T-PRF is poised to play a crucial role in improving clinical outcomes and advancing the practice of dental medicine.

However, further research is needed to standardize protocols, evaluate long-term outcomes, and compare T-PRF with other regenerative materials.

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