Review Article

Comparative evaluation of open flap debridement therapy with two different types of platelet concentrates (mention the names) as adjuncts- A Systematic Review.

Running Title: Platelet concentrates in regeneration

Abstract:

Background (delete) Conventional Periodontal therapy such as scaling and root planning (spelling) and [open flap debridement (OFD-no need to mention short forms in abstract] aims to halt the inflammation process and promotes repair of disease-related defects. Current regenerative procedures offers a limited potential toward attaining a complete periodontal restoration and none is considered a gold standard in the treatment of intrabony defects. [Platelet rich fibrin (PRF)], an autogenous biomaterial combines the fibrin sealant properties along with growth factors and cytokines entrapped in a fibrin matrix thereby providing an ideal environment for wound healing and regeneration of tissues. In recent times it has been used various disciplines in dentistry in a wide range of treatment modalities (shift to introduction). This study was done to compare the efficiency of Titanium-PRF and Leukocyte-PRF adjuncts to OFD therapy to treat intra-bony periodontal defects.A search was conducted through PubMed and various other databases such as Cochrane, Google Scholar and EBSCO Host , under the key words, OFD , T-PRF,L-PRF, Clinical Outcomes, Comparison and Randomised Contolled Trials. Six relevant articles were selected for analysis. From the comparison and analysis (mention the findings) we can conclude that T-PRF has better properties, greater bone defect fill and defect resolution as compared to L-PRF.

Key words: Regeneration, Open Flap Debridement, Titanium-PRF, Leukocyte-PRF, intra bony defects

Introduction:

A multifactorial inflammatory disease destroying the hard and soft tissues of the periodontium, is known as Periodontitis(reference). Periodontal therapy aims to eliminate the inflammation process and promote bone and tissue healing. The purpose of said conventional therapeutic measures is to reduce Pocket probing depth(PPD) and increase Clinical attachment level(CAL).It unfortunately, cannot bring back the lost alveolar bone, which then leads to periodontal regenerative therapy to repair the intra-bony defect. Periodontal regeneration is a complex multifactorial process involving biological events such as cell adhesion, proliferation, and differentiation in a sequential manner (Chen F-M and Jin Y, 2010).reference Among the techniques used to manage residual pockets after cause related therapy OFD (full form) has been considered as standard and one of the earliest modality(Mishra PRN et al ., 2019). reference

Several regenerative materials have been looked at for the management of intra-bony defects such as; bone grafts/ bone substitute materials,guided tissue regeneration (GTR), growth factors and enamel matrix derivative. Current regenerative therapies can only restore a fraction of the original tissue volume thus inferring a limited potential in attaining complete periodontal restoration.(discussion) Consequently the quest on devising an autologous bioactive material that is most effective in its regenerative potential had been escalating. The Choukroun's Platelet-rich fibrin(PRF) is one such product that has proved its worth in terms of accelerated wound healing and regeneration. reference

Ehrenfrest et al; in his study showed that PRF induced a significant and continuous stimulation and proliferation of gingival fibroblasts, dermal pre-keratinocytes, pre-

adipocytes, and maxillofacial osteoblasts (Dohan Ehrenfest DM et al., 2009). reference Platelet concentrates are better than any other biomaterial as there is a slow release of several factors such as;leukocytes, vitronectin, fibronectin, Bone morphogenetic proteins (BMPs), and cytokines that help in quicker healing and regeneration (Panda s et al,.2019; (shift to discussion) http://dx.doi.org/10.3390/ijms20061347-delete

Initially, PRP was combined with various Bone Grafting materials which gave a satisfactory result. But due to risk of antigenicity by the presence of bovine thrombin, [Leukocyte-PRF(L-PRF)] was introduced by Choukroun in 2001.In studies conducted by Sharma et al, and Pradeep et al; it was repeatedly proven that autologous PRF had excellent healing abilities, due to the constant slow release of growth factors (Sharma et al.,2011). reference However, controversies regarding silica cross contamination were raised by O'Connell and Tunali et al; the focus shifted towards a new bio material(O'Connell SM,2007;Tunali et al., 2013). Reference (shift to discussion)

Titanium was brought into focus due to its osteointegration, heamatocompatibility and superior properties of platelets on activation. Keeping this in mind, newer products likeTitanium-PRF(T-PRF) should be tried as an adjunct to open flap debridement therapy, as titanium provides adjunctive properties to PRF. T-PRF is based on the principle that titanium tubes could be more effective in activating platelets than glass. It helps in enhancing the haematocompatibilty of the material, which further facilitates the formation of a more polymerized fibrin network (Tunali et al., 2013). reference L-PRF on the other hand, is made without any added anti-coagulants. In this method, platelets and leukocytes are collected with high efficiency and leukocytes are intact throughout. Platelets are activated by silica from the glass tubes. L-PRF improves the preservation of the alveolar width resulting in less overall bone loss than in natural bone healing (Panda s et al,.2019)reference

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Very few studies have been conducted using T-PRF as an adjunct along with Open Flap Debridement to heal periodontal intrabony defects. This systematic review aims to collect all available and relevant data from standardized sources and compare the efficiency of T-PRF and L-PRF as adjuncts to open flap debridement therapy to treat intra-bony periodontal defects

Materials and Methods:

All articles were searched using the [PRISMA(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)] guidelines (Stewart LA et al.,2015). (Figure 1)

Eligibility Criteria:

For the inclusion of articles in this study, the PICOS guidelines (Figure 2)(Methley AM et al ., 2014) were followed which were as follows; comparative studies of either T-PRF and L-PRF as adjuncts with open flap debridement surgery, individual comparisons of T-PRF and L-PRF with other standard material as adjuncts, randomised control trials comparing either the two materials with each other or individually with other standard materials. reference

Exclusion Criteria:

Any letters to the editor, abstracts and articles in other languages were excluded.

Outcome:

The outcome of this systematic review is to collect all the full text data and compare the clinical efficiency of T-PRF and L-PRF as adjuncts to open flap debridement surgery to manage intra-bony defects.

Method of Preparation:

T-PRF:

A blood sample is collected from a willing volunteer. 10ml blood is transferred into a Grade IV titanium tube. The tube is immediately centrifuged with a specific table centrifuge at room temperature. It is centrifuged at 3500 rpm for 15 min(Tunali's Protocol) clockwise(Tunali et al., 2013).

L-PRF:(Dohan DM et al., 2006): reference

Choukroun's PRF protocol is a simple and free technique developed in France by Choukroun et al in the year 2001. It is considered to be a second-generation platelet concentrate because, natural concentrate is produced without anticoagulants. Blood is collected in dry glass tubes and centrifuged at low speed 2800 rpm for 12 min (Process protocol, Nice, France). reference In the absence of anticoagulants, platelet activation and fibrin polymerization are triggered immediately. The PRF clot forms a robust fibrin matrix with a three-dimensional architecture, in which most of the platelets and leukocytes from the collected blood are concentrated. When pressed between two gauzes,the PRF clot becomes a strong membrane.

Search Strategy:

An electronic search was conducted in the PubMed/MEDLINE database, and other sources such as Cochrane Database, EBSCOHost and Google Scholar, with the following key words; Titanium enriched PRF, Leukocyte and Platelet Rich Fibrin, Open Flap Debridement, Periodontal Disease, Intrabony Defects, Comparative studies, Randomised Control Trials. A total of 6 full text records were selected for this study ;(Table 1).

*Risk of Bias (Armijo-Olivo S et al., 2012)***:**

Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials was used to evaluate the risk of bias. Critical assessments were made separately for different domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each domain, the risk of bias was graded as high, low, or unclear based on criteria described in the Cochrane Handbook for Systematic Reviews of Interventions.

*Observations and Results***:**

From the above comparison it is clear that titanium activated platelets have more potential for healing and regeneration than leukocyte activated platelets. They show a marked increase in CAL and reduction in the PPD. They also show greater bone defect fill and resolution. Therefore, T-PRF proves to be much superior in its properties than L-PRF.

Results missing tables required

Discussion:

In our study we compared the conventional L-PRF and the novel T-PRF as adjuncts to OFD to heal intra-bony defects. We included in vitro and in vivo comparative studies, prospective and retrospective studies as well as randomised controlled trials for the same. After screening all available records, six relevant randomised controlled trials were selected for the analysis.

The main treatment modality chosen was open flap debridement. The aim of this procedure is to reduce the PPD and increase the CAL. This procedure includes well-defined incisions, flap reflection and an atraumatic procedure, whose primary goal is healing (long junctional epithelium) of the periodontal pocket with minimum tissue loss (Rateitschak KH et al ., 1989). reference Because the alveolar process is only partly exposed, post-operative pain and swelling are rare. The main goals of the procedure include optimum mechanical subgingival root planing and "decontamination" with direct vision followed by healing (primary intention) (Rateitschak KH et al., 1989). reference

According to a recent systematic review, the average CAL gain seen with OFD by itself was 1.65 mm, average PPD reduction was 2.80mm, gingival recession (REC) increase was 1.26 mm and bone gain at 12 months was clinically 1.04 mm and radiographically 0.95 mm(Graziani F et al.,2012-very old). reference

The method of preparation of both products, T PRF and L-PRF are almost the same, with the only difference that T-PRF is produced in tubes coated with titanium. Therefore, titanium grants better properties to the platelets in the PRF produced. L-PRF is produced without any additional anti-coagulants and is only activated by the silica in the glass tubes. It has been proven to be a successful adjunct by various authors over the years. reference

In a study conducted by Pradeep AR et al; they concluded that autologous PRF (L-PRF) had better bone defect fill and resolution than the peptide enhanced bone graft(Sharma A and Pradeep AR, 2011). In another study conducted by the same author in the year 2012, he concluded that autologous PRF (L-PRF) and the PRP groups proved to be better adjuncts to open flap debridement than just doing open flap debridement. Amongst the two materials, L-PRF proved to be superior to PRP (Pradeep AR, 2012). reference In a study conducted by Mathur A et al(Mathur A et al ., 2015); it was proved that L-PRF had better healing and bony defect resolution properties after open flap debridement, than Autologous Bone Graft(ABG). reference These studies showed that autologous PRF has been a successful adjunct to OFD over the years.

T-PRF on the other hand, is a relatively new product, and is also relatively expensive for research purpose as compared to L-PRF. Therefore, not many studies have been conducted for the same. Chatterjee A et al (2017); it was seen that T-PRF proved to be a better adjunct to Open Flap Debridement, than autologous PRF(Chatterjee A et al ., 2016). reference There was a marked regaining in attachment as well as other clinical and radiographic parameters. Mitra DK(2019) showed that, T-PRF and L-PRF had similar clinical results but histologically, T-PRF produced a thicker fibril network (Mitra DK et al., 2019). reference Our study therefore, is in accordance with these studies where our end result was also that T-PRF had superior properties as compared to L-PRF, and therefore made a better adjunct to Open Flap Debridement to manage Intra-bony Defects.

Conclusion:

L-PRF(Choukroun's PRF) has been a successful adjunct over time. Its resorption rate however, is very high. Conversely, T-PRF, has a lower resorption rate and higher haemato-compatibilty and other superior properties compared to L-PRF due to titanium activated platelets. Further research needs to be conducted on the clinical outcomes of both adjuncts individually and more split mouth trials need to be conducted comparing the two materials as adjuncts to have a more homogenous and standard data.

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Annexure-1:

Figure 1: PRISMA guidelines toperform the record search; Search Strategy

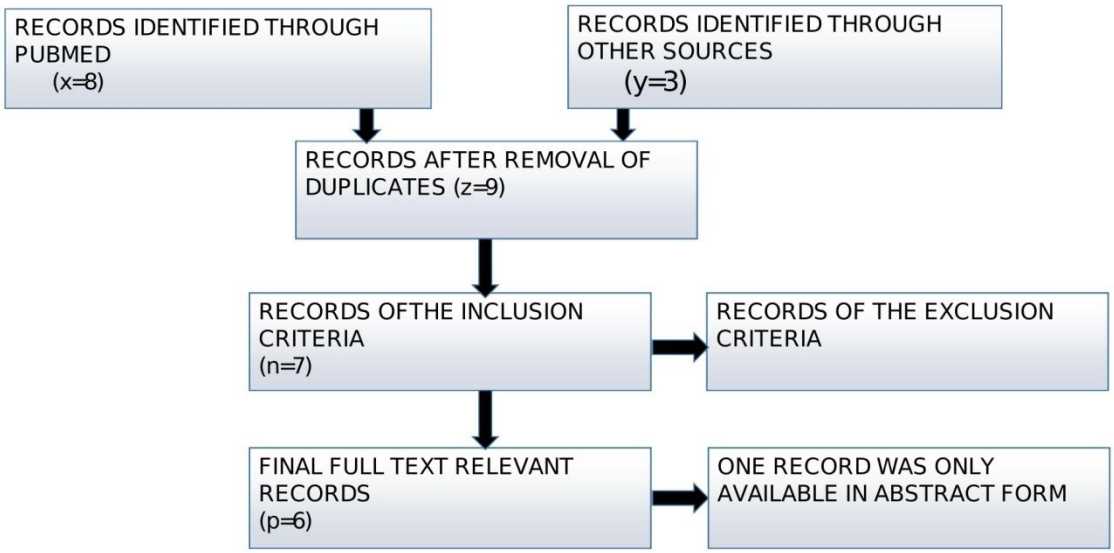

Figure 2: PICOS guidelines for deciding the Inclusion Criteria

P (POPULATION)	PERIODONTAL DISEASE LEADING TO INTRABONY DEFECTS
I (INTERVENTION)	OPEN FLAP DEBRIDEMENT
c (COMPARISON)	T-PRF AND L-PRF AS ADJ UNCTS TO OPEN FLAP DEBRIDEMENT SURGERY
O (OUTCOME)	BETTER DEFECT FILL AND RESOLUTION
S (STUDY DESIGN)	RANDOMISED CONTROL TRIALS, SPLIT MOUTH CLINICAL TRIALS, IN VIVO AND IN VITRO COMPAATIVE STUDIES, PROSPECTIVE AND RETROSPECTIVE STUDIES

*Annexure 2:*Table 1: Characteristic table:

Name	Author/Year	Type of Study	Type of PRF Compared	Results
Clinical effectiveness of autologous platelet-rich plasma and peptide-enhanced bone graft in the treatment of intrabony defects.	Pradeep A et al 2009[11]	Randomized Controlled Trial	L-PRF compared to Peptide -enhanced bonegraft	CT revealed a greater defect fill for the L-PRF group
Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of 3-wall intrabony defects in chronic periodontitis: A randomized controlled clinical trial.	Pradeep A et al; 2012[12]	Randomized Cotrolled Trial	L-PRF compared to PRP	Greater mean percentage of bone fill was found in the L-PRF group as compared to the PRP group
Evaluation of	Mathur A el al; 2015[13]	Randomized Controlled	L-PRF compared to Autologous Bone Graft	Greater defect fill and resolution was

intrabony defects treated with platelet-rich fibrin or autogenous bone graft: A comparative analysis		Trial		seen for the PRF with Open flap debridement group thanwith the ABG group
Treatment of periodontal intrabony defects using autologous platelet-rich fibrin and titanium platelet-rich fibrin: a randomized, clinical, comparative study.	Chatterjee A et al; 2017[14]	Randomized Controlled Trial	L-PRF compared to T-PRF	T-PRF showed better defect fill and defect resolution that L-PRF.
Comparative study using autologous platelet-rich fibrin and titanium prepared platelet-rich fibrin in the treatment of	Mitra DK, et al; 2019[15]	Randomized Controlled Trials	L-PRF compared to T-PRF	T-PRF and L-PRF showed similar healing and resolution of bone defects, but histologically T-PRF showed a

infrabony defects: An in vitro and in vivo study.				thicker fibril network
Comparison of GTR, T-PRF and open-flap debridement in the treatment of intrabony defects with endo-perio lesions: a randomized controlled trial	Ustaoğlu G, et al; 2020[16]	Randomized controlled study	T-PRF and open flap debridement, compared to Guided Tissue Regeneration, compared to only Open Flap Debridement	T-PRF group showed maximum healing and resolution of defect.