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A Literature Review into the Mechanisms and Uses of Platelet Rich Fibrin in Periodontology. Is it Effective?

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Introduction

Healing following surgical procedures is an intricate process, involving a complex interplay of cellular and host factors. In the last 50 years, there have been great strives to develop materials to aid this healing process, one of which is platelet-rich fibrin (PRF). However, it has been on the market for 20 years, and despite being hailed as a breakthrough in regenerative medicine, it appears not to have been widely utilised in the field of Periodontology, especially in Europe. This literature review intends to explore the reasons for this, as well as comparing PRF to available alternative materials.

Before exploring the mechanisms of action of PRF and its predecessor platelet-rich plasma (PRP), it is important to have a basic grasp of the biological mechanisms of tissue healing. There are four key aspects of wound healing[1]:

1. Haemostasis
2. Inflammation
3. Proliferation
4. Maturation

Each aspect incorporates differing cell types as shown in Figure 1:

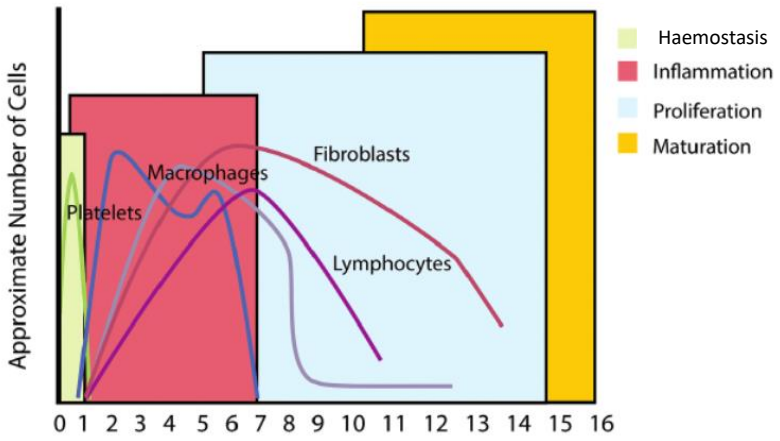

Fig 1: A chart displaying the various cell types involved in tissue healing.[1]

These four aspects are not separate phases, and there are periods of overlap, as displayed in the diagram above. An ideal biomaterial that is aimed at enhancing the efficiency of the regenerative

process would target all four components, however, no such artificial material exists on the market as of the date this paper is being written. The main disadvantage of current regenerative biomaterials is that many are avascular, and without a blood supply they lack the biological basis to achieve complete regeneration of human tissues[2].

It is important to note in this diagram the important role of platelets in haemostasis. Platelets are the primary component of the initial haemostatic clot, and they form a scaffold for the secondary fibrin clot. Besides their role in haemostasis, platelets secrete a wide number of proteins including platelet-derived growth factor (PDGF), transforming growth factor- β1 (TGF-β1), fibronectin and fibrinogen[3]. Through the release of these proteins, platelets activate and regulate the other cells involved in the remaining three aspects of tissue healing. If researchers were able to create a material utilising platelets, they would have a substance capable of targeting all four aspects of wound healing. This led to the search for platelet-derived preparations.

Platelet Rich Plasma

The first material to come about from this research was Platelet Rich Plasma (PRP). It was developed in the 1970s and consists of an 'autologous concentration of platelets in concentrated plasma' [4]. There are several ways to formulate it, with no real consensus being met on the best protocol. All preparation methods begin with obtaining a sample of the patient's blood through venepuncture. Each component of blood has a different weight, and therefore when placed in a centrifuge, it separates into different layers [5]. There are two separate spin speeds used to obtain the final product: the first spin, or soft spin, is slow and separates the erythrocytes. The remaining plasma is then subjected to a second spin, the hard spin, which is at a significantly higher speed to obtain the platelet concentrate[6].

Platelets naturally aggregate to each other and activate, and this has a negative effect on the function of PRP [7] and the release of the key growth factors described above. Therefore, PRP requires the addition of citrate and bovine thrombin as anti-coagulants. Citrate binds to calcium in the blood, thus preventing the coagulation cascade. It typically takes 30 minutes to 1 hour to prepare[8]. These artificially added anti-coagulants are then introduced to the surgical site along as a component of the PRP and can interfere with haemostasis.

A fundamental disadvantage of PRP is that it is a liquid, and to be used effectively, it must be combined with allogenic or xenogeneic materials to form a stable substance. This incurs an expense, but also leads to difficulties obtaining approval from regulatory agencies[9].

The release of PGDF modulates tissue repair and increases the speed of the wound healing process[10]. A study by Kobayasha et al[11], showed that PRP releases growth factors within the first 60 minutes of placement and very little after that. The study demonstrated that a steady release over a prolonged length of time is preferential for wound healing. The disadvantages described led to the search for new materials.

The Dawn of Platelet Rich Fibrin

In 2001 in France, a breakthrough was made: Choukroun et al [12] made a stark discovery in that if a lower centrifugal speed was used in a one stage process (12 minutes at 2700rpm), without the use of anticoagulants, then the formulation contained a fibrin scaffold which was termed PRF. The fibrin scaffold acted as a provisional extracellular matrix. This gave the material a semi-solid formulation, which allowed for easy manipulation, but it was also entirely autologous.

The fibrin scaffold not only trapped platelets but also leukocytes which released further proteins, many of which were not seen in PRP. Not only this, but leukocytes are naturally one of the first cells to reach a healing surgical site [13], so PRF leads to a higher initial concentration of these leukocytes, which subsequently has been shown to reduce the incidence of post-operative infections[14].

PRF can be thought of as consisting of 3 main components[15]:

1. Cellular: The fibrin scaffold traps both Leukocytes and Platelets
2. The provisional extracellular matrix: this is the fibrin scaffold.
3. Bioactive molecules: the most significant being PGDF and TGF-β1

Angiogenesis is an important component of wound healing, and research by Dohan et al [16] demonstrated the role of leukocytes through their release of Vascular Endothelial Growth Factor (VEGF). This growth factor stimulates angiogenesis through its regulation of endothelial cell proliferation, migration, and specialisation. Platelets also release VEGF, so a small amount is present in PRP, however, it is seen in much higher concentrations in PRF due to the leukocytes.

So, to summarise, when comparing PRF to PRP:

- PRF does not require the addition of anti-coagulants or artificial bone-grafting materials.
- It is semi-solid because of the presence of a fibrin scaffold.
- It contains leukocytes as well as platelets.

Preparation Protocols for PRF

The preparation protocol is simple[17]:

1. 5ml of prepared blood is collected via venepuncture.
2. The blood is placed in a sterile vacutainer tube of 6ml capacity.
3. The blood sample is placed in a laboratory centrifuge at 2700rpm for 12 minutes.

After a short period, the sample settles and it will be seen to have divided into 3 distinct layers: a red lower fraction containing erythrocytes, a middle fraction containing the fibrin clot (PRF), and an upper straw-like fraction containing cellular plasma. Fig 2[18] below shows these layers.

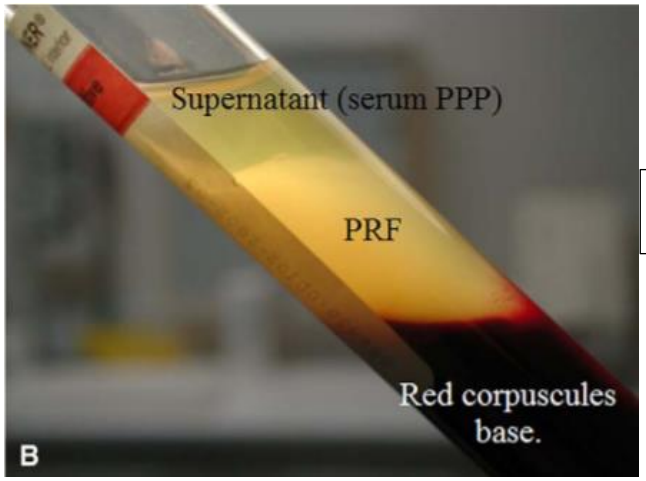

Fig 2: A image showing the 3 distinct layers seen after the centrifugal process.

The upper fraction is removed, and the middle fraction containing PRF is then collected. The whole process should take no longer than 20 minutes, compared to 30 minutes to 1 hour for PRP[8]. The PRF must be used quickly, as without the addition of an anti-coagulant, the PRF can coagulate to a clinically unusable level within 3 minutes[17].

Inclusion Criteria for the Literature Search

A broad search of the literature has been conducted for the following sections of this literature review according to the defined PICO detailed below:

- Population: adults over the age of 18 who are systemically healthy but affected by moderate to severe (Stage II-IV) periodontitis or are undergoing surgical periodontal procedures.
- Intervention: Platelet Rich Fibrin used as part of a surgical procedure.
- Comparison: artificial membranes and grafting materials, or no membrane or grafting material.
- Outcome: reduction in pocket probing depths, increases in the efficacy/speed of bone formation or more favourable healing outcomes.

Studies that do not meet the defined criteria will not be included in the discussion.

Applications of PRF in Periodontology

PRF can be manipulated into a membrane by compression between 2 sterile pieces of gauze[19]. This conversion into a membrane allows PRF to be widely utilised in surgical periodontal procedures. PRF membranes have shown favourable properties when compared to other artificial membranes, such as their ability to release PGDF and other growth factors for up to 28 days following placement[20].

The use of PRF in the Treatment of Infra-bony Defects.

Chang et al[21] investigated the use of PRF membranes in the surgical management of periodontal infra-bony defects. It can act as a resorbable membrane in the guided tissue regeneration (GTR) process, preventing the formation of the long junctional epithelium and the migration of non-desirable cells. Chang et al[21] described the key role of periodontal ligament fibroblasts (PDLFs) in this GTR process, through their ability to stimulate osteoblastic deposition of bone. PDLFs also display high alkaline phosphatase activity, which seems to have a role in the deposition of acellular cementum[22]. Chang et al[21] conducted a case series using six systemically healthy patients with infra-bony defects measuring greater than 5mm pocket probing depths. The defects were treated via conventional access-flap surgery, and PRF was placed as a membrane and the flap was sutured closed. Three weeks postoperatively an average of 2.25mm clinical attachment gain was seen. However, there was no control group, and the study size was small.

Tsai et al[23] found that PRF stimulates PDLF proliferation, as well as osteoblast and gingival fibroblast proliferation by 1.28-fold collectively ($P<0.05$)- subsequently increasing post-operative bone regeneration. However, they were unable to determine the mechanism by which PRF causes this. Further research is required to determine this mechanism and improve the quality of the evidence surrounding the effect of PRF on infra-bony defects. A conclusion or recommendation cannot be drawn on this treatment modality at the current time.

The effect of PRF on Healing following the Harvest of Free Gingival Grafts from the Palate.

PRF has also been used to aid wound healing following the harvesting of a free gingival graft. Kulkarni et al[24] performed a randomised clinical trial (RCT) to investigate the effects of PRF following the harvest of a free gingival graft from the palate. They used 18 systemically healthy patients, 10 of whom had PRF placed palatally to aid healing, whilst 8 had a periodontal pack placed to act as a control group. After 14 days complete wound closure was seen in the PRF group, whilst on the 14th-day incomplete wound closure and inflammation was seen in the control group. This demonstrates the favourable role of PRF in wound healing, however, the sample size was small, and no quantitative data was taken so the results were subjective. Furthermore, no P values were given to determine if the results were statistically significant.

Meza-Mauricio et al[25] conducted a systematic review to analyse the research into the effectiveness of PRF in aiding the healing process following this harvesting. They found only 9 relevant randomised controlled trials investigating this intervention, all of which supported the use of PRF for this application. The authors concluded however that further research must be done on the topic to give clear recommendations.

The use of PRF to enhance Osseointegration Post-Implant Surgery.

Perhaps the most common use of PRF is in aspects of implant surgery. A comprehensive paper is available on the topic by Simonpieri et al[26]. It discusses the potential for PRF to hasten the osseointegration process following implant placement, through the release of PGDF and other growth factors, which play key roles in bone healing. A search for evidence revealed a study by Öncü et al[27], which placed 4 implants in 12 white rabbits. Two of these implants were soaked in PRF before placement, with the other two being acting as controls. The results showed that PRF increased bone formation surrounding the implants by 31.7% compared to the control group. However, the study size was small, and the results cannot be extrapolated to human subjects.

The above study was followed up by the same authors in 2015[28], with an RCT, but this time using twenty human patients. The patients had 2 implants placed in each in the sites of teeth that had been extracted 6 months previously. The extent of osseointegration was judged using mean implant stability quotients (ISQ). They found that the mean ISQ for implants placed with PRF was 6 points higher than the control group after 4 weeks ($P<0.002$). ISQ does not directly correlate to the degree of osseointegration, and the lack of histological analysis to quantify the results limits this study.

Castro et al[29] conducted a systematic review of the literature surrounding the effect of PRF on osseointegration following implant placement. They concluded that the studies suggest that there is a benefit to the use of PRF in enhancing osseointegration. However, they also concluded that the discrepancies in the variables measured between the studies justify the need for further RCTs to conclude the evidence.

The use of PRF in Sinus Lift-Procedures

Another application of PRF in implant surgery is to aid bone formation after the sinus-lift procedure. This procedure involves two surgical procedures: firstly, lifting the Schneiderian membrane following a partial maxillary osteotomy to create an artificial cavity below the maxillary antrum[26]. This site is usually filled with an artificial grafting material such as emdogain to regenerate bone, hence allowing implants to then be placed in a second surgical procedure six months later. Peleg et al[30] describes sinus lifting and implant placement in a one-step surgical procedure, by which the implants

themselves act as 'tent pegs' to maintain the height of the artificial cavity. In this procedure, it is favourable to fill the cavity with a blood clot and an allograft to reduce the risk of failure, and PRF may act to reinforce this clot. Very little literature is available with regards to the use of PRF in a one-stage approach.

In the studies described above to investigate implant osteointegration following the use of PRF, a limitation was the inability to perform histological analysis of bone due to ethical issues surrounding its collection. However, the use of PRF in the sinus lift procedure potentially allows for the collection of human bone samples during the implant placement if a two-stage surgical procedure is used. A trephine drill can be used during implant placement to collect human bone, which would be lost regardless[26].

Choukroun et al[31] performed a non-randomised control trial to investigate the effects of PRF on bone regeneration following the placement of a graft as part of a sinus lift procedure. The trial involved nine patients undergoing sinus-lifting and implant placement as two separate procedures. The grafting material used was freeze-dried bone allograft (FDBA), which in six of the patients, was reinforced with PRF. The control group, consisting of 3 patients, received a graft containing FDBA only. A sample of bone was harvested at the implant placement procedure after 4 months, and this underwent histological examination. However, the author stated that the control group's graft had not undergone sufficient maturation to be harvested at 4 months, so instead in this group, the bone was harvested at 8 months. The results revealed that the histological composition of bone was similar between the two groups, however, FBDA combined with PRF resulted in faster bone maturation. The quality of this evidence is weak. There is a conflict of interest present as Choukroun, the author of this study, was the researcher that developed PRF. Also, the inability of the researchers to harvest bone from both groups at the same time makes the findings difficult to interpret. Further studies are required to determine if PRF is effective in this application before drawing recommendations.

Regeneration of Peri-Implant Bone Defects using PRF.

Simonpieri et al[26] also described the use of PRF to regenerate peri-implant bone defects. These bone defects are largely the result of peri-implantitis, which is described by Berglundh et al[32] as 'a site-specific pathological condition characterised by the inflammation of the peri-implant soft connective tissue and progressive loss of implant-supporting bone'. This leads to what is described as a 'peri-implant bone defect'. In a study by Schwarz et al[33] it was observed that all moderate to severe cases of peri-implantitis resulted in a peri-implant bone defect.

Schwarz et al[33] also created a classification system for the defects: Class I defects resembled conventional periodontal infra-bony defects, whilst class II defects presented as horizontal bone loss surrounding the implants. A study by Wehner et al[34] in 2020 observed and classified 193 peri-implant bone defects associated with peri-implantitis. They found that 49.2% were class I defects, 17.1% were class II defects, and 18.7% did not fit the Schwarz classification. Interestingly, no studies are available using PRF to regenerate bone in peri-implant defects in which this classification was used. This highlights the need for further research to determine the significance of the type of defect on the effectiveness of PRF in this field.

Several studies are available which do not use the Schwarz classification. Ding et al[35] investigated the use of adipose-derived stem cells (ASC) sheets in combination with PRF to regenerate bone in peri-implant bone defects. The randomised clinical trial was performed on 9 adult beagle dogs. Their third and fourth mandibular premolars were extracted and then bone defects were created in the mesial sockets using bone drills before implant placement. The dogs were randomly assigned to four groups: group A had ASC sheets only, group B received ASC sheets in combination with PRF, group C received PRF only and group D received no treatment. The animals were sacrificed four weeks after surgery and a micro-CT system was used to scan the bone containing the implants, before being sent for histological analysis. The results showed that new bone was formed in the peri-implant defect in all four groups. The group that received PRF and ASC sheets showed the most bone regeneration with 5% more bone fill than the other groups shown during histological analysis. However, this study was an animal test, so it is challenging to extrapolate the results to humans. Moreover, the author failed to declare the number of beagles in each group, and no analyses of statistical significance were performed. Also, the defects were artificially created, rather than a result of peri-implantitis.

Another study by Lee et al [36]showed similar results. They used eight 4-month-old white rabbits, which underwent surgery during which two implants were placed 5mm apart. Prior to implant placement, bone was removed using a bone drill to simulate a peri-implant bone defect. One implant in each rabbit was covered in PRF, whilst the other was left unfilled to act as a control group. After 8 weeks the animals were sacrificed and the bone containing the implants was sent for histological analysis. The results showed 29.30% new bone in the PRF compared to 11.06% in the control group, which was statistically significant ($P<0.02$). This supports the hypothesis that PRF is successful in enhancing bone regeneration of peri-implant bone defects, however, there were limitations to the study. Yet again, animals were used in this experiment, so the relevance of the results is questionable. Also, the PRF was prepared using Eppendorf tubes, compared to the conventional glass tubes described by Choukroun[1]. The glass tubes are essential to prevent early coagulation[17], so this could reduce the validity of the findings.

A systematic review would be useful to generate recommendations for the use of PRF in this scenario. It is impossible to draw recommendations from the studies above considering their limitations- the main one being that they are animal studies. Human studies are ethically questionable to investigate PRF in this intervention due to the need to obtain bone samples from live specimens.

Preservation of the Height of the Alveolar Ridge using PRF following a Tooth Extraction.

Whilst tooth extraction is not necessarily a periodontal procedure, the alveolar bone loss seen following a tooth extraction presents a challenge for implant placement if it is particularly severe. Not only that, but the loss of the alveolar ridge also presents a challenge to prosthodontists who are seeking to provide removable prostheses. There is a potential that PRF could be used to preserve the height of the alveolar ridge and prevent this progressive bone loss[26].

Zhang et al[37] performed a non-randomised control trial using 28 patients undergoing tooth extraction. Patients were assigned into the control or experimental group according to their wishes resulting in a total of fourteen participants in each group. In the experimental group, the socket was filled with PRF following the extraction. In the control group, the socket was left unfilled. CBCT scans were taken 3 months later just prior to implants being placed at the site of the extractions, and the bone was harvested and sent for histological evaluation. It was found that the experimental group had significantly more newly formed bone than the control group. The CBCT scans revealed an osteoid area of 9.7624% in the experimental group, compared to 2.8056% in the control group ($P<0.01$). They also found that alveolar bone height was higher after 3 months in the experimental group, however, this was not statistically significant. Therefore, it is impossible to reach a conclusion with regards to the effects of PRF on the preservation of alveolar ridge height from this study.

A randomised clinical trial performed by Azangookhiavi et al[38] aimed to compare the effects of PRF and FDBA on the preservation of the alveolar ridge following tooth extraction. The trial contained 32 participants all undergoing extraction of non-molar teeth of hopeless prognosis. The first group of 16 participants had PRF placed in the socket following extraction, whilst the second group of 16 participants had FDBA placed to fill the socket. Bone resorption was measured immediately after the surgery and 12 weeks later using a periodontal probe and acrylic stent which was fabricated from the patient's alveolar ridge pre-operatively. The results demonstrated that both groups showed a statistically significant reduction in ridge width, however, there was no statistically significant difference in efficacy between FDBA and PRF. This allows us to conclude that PRF and FDBA are both of similar efficacy in preserving the alveolar ridge following a tooth extraction, however, the lack of a

control group in this trial makes it impossible to conclude as to whether either is effective in this scenario.

A split-mouth randomised control trial was undertaken with regards to this intervention by Temmerman et al[39]. The trial contained 22 participants in need of symmetrical bilateral tooth extractions. After the surgery, the sockets were cleaned and randomly assigned to the experimental group or control group. Those sockets in the control group were left to heal naturally, whilst those in the experimental group were filled using PRF. A CBCT was taken at baseline immediately after the extractions, and then again after 3 months. The results showed that resorption in the control site measured 1.5mm vertically, compared to 0.5mm vertically in the experimental group P(<0.005). A similar trend was seen in ridge width, with a 51.92% reduction seen in the control group, compared to 22.84% in the experimental group P(<0.005). These results support the use of PRF to preserve the alveolar ridge following dental extractions. This study was peer-reviewed and there were no conflicts of interest, so the quality of this evidence is strong.

To summarise PRF appears to be beneficial with regards to this intervention, however, there are no systematic reviews available to pool the data and provide definitive recommendations.

Potential Barriers to the use of PRF in Periodontology

Whilst being hailed as a 'wonder material' by many in the field of Dentistry, PRF is not devoid of challenges and disadvantages. Whilst this technique has been available for over 20 years now, one of the fundamental flaws is that it's biological mechanisms are still not fully understood[40]. It is of critical importance that these mechanisms are extensively researched before their potential use in newly discovered applications. The use of PRF with current clinical and biological knowledge may present an ethical issue, however, it can be argued that as the preparation is entirely autologous, the risks are minimal which subsequently negates the ethical challenge.

As PRF is an entirely autologous material, it is difficult to generate in large quantities. This restricts its use in more extensive surgical procedures, as it would not be possible to completely cover the surgical site with such a limited quantity[41]. Furthermore, this autologous nature limits the use of PRF to solely the donor patient themselves. It is not possible to use PRF as an allogenic material due to the high concentration of leukocytes within the fibrin mesh, which would quickly attack and damage the recipient's tissues. Alternatively, due to the highly antigenic nature of these cells, the recipient's immune system could attack the graft[41].

The preparation of PRF requires additional equipment and a confident clinician[40]. An operator must have access to a laboratory centrifuge, and blood collection equipment. Furthermore, the clinician

must be confident in venepuncture, which is not extensively taught at undergraduate level. Not only this, but venepuncture can represent a source of anxiety for patients who are already potentially experiencing high levels of stress due to the surgical procedure. Generation of PRF is technique sensitive requiring careful and quick handling by the clinician, as it begins to coagulate to clinically unusable levels within 3 minutes[40]. Glass coated tubes must be used to slow down this coagulation process[42]. The use of glass-coated tubes may pose problems, as there have been reports of silica particles from the glass being suspended within the PRF[43].

The centrifugal process is somewhat confusing, with several studies using different procedures to generate PRF and inaccurately reporting their relative centrifugal force (RCF) values. This led to Miron et al[44] creating a standardised protocol for the centrifuging process, which aims to alleviate this confusion. This has led to the easier cross-comparison of studies as the vast majority now use this protocol. Clinicians must ensure they follow the pre-determined procedure to generate an optimal sample of PRF.

Very little research has been undertaken with regards to the use of PRF in patients with coagulation disorders or those on anti-coagulant medications. The presence of a fibrin scaffold is a critical component of PRF, so logic dictates that these conditions will affect its function. Studies must be conducted to determine these effects. It has been suggested that coagulation disorders resulting from low platelet numbers may have the greatest effect on the efficacy of PRF[45].

Current Research into PRF

Titanium Platelet Rich Fibrin (T-PRF)

As discussed above, one of the drawbacks of PRF is the potential for silica particles from the glass tubing to remain suspended in the product. This led to Tunali et al[46] researching with titanium coated tubes instead- which was coined as T-PRF. Titanium has a similar effect to glass in that it can activate the platelets, and they hypothesised that it may be more effective with regards to this activation.

A non-randomised trial was therefore conducted by Tunali et al[46] in which they collected 18 mL of blood from 10 healthy male volunteers. They then placed 9ml of blood into a titanium coated tube to produce T-PRF, and the other 9ml into a glass-coated tube to produce conventional PRF. The samples then underwent histological analysis using a scanning electron microscope (SEM). They found that the T-PRF fibrin scaffold covered a larger area than the conventional PRF ($P<0.05$), and

that platelet aggregation was similar in both the groups (P<0.05). Therefore, titanium may have the effect of creating a more polymerised fibrin scaffold, but the results of this study do not indicate it is more effective in the activation of platelets. The sample size of this study was small, and to draw clear comparisons, another study is needed with more participants. Also, there is a conflict of interest in that Tunali et al developed T-PRF and conducted this research.

Injectable Platelet Rich Fibrin

Since the introduction of PRF in 2001, there have been several attempts to modify its structure and manufacture new formulations. One of these recently developed formulations is injectable-PRF (iPRF) which was introduced by Miron et al[47] in 2017. This is produced by utilising shorter and slower centrifugal speeds. The result is i-PRF, a liquid formulation, which can be injected into the surgical site. Its liquid nature allows for easy handling and straightforward combination with current biomaterials. Furthermore, it has been shown that i-PRF contains circulating stem cells, which may enhance its regenerative potential.

Karde et al[48] performed a study to evaluate the platelet count and anti-microbial efficacy of i-PRF in comparison to PRF and PRP. Ten patients with gingivitis were selected and 8ml of blood was collected via venepuncture. Two millilitres of each sample were then used to produce i-PRF, PRF and PRP. The remaining 2ml was left as a control. Tests were then conducted to generate the platelet count, and an agar plate containing a plaque sample from the patient was incubated with the respective platelet preparation. The platelet count for i-PRF was found to be 91000/mm^3 higher than PRP and 1143000/mm^3 higher than PRF (P<0.001). Antimicrobial efficacy was demonstrated by a zone of inhibition surrounding the platelet samples on the agar plate. It measured 1.42cm in i-PRF compared to 1.3cm and 1.02cm in PRF and PRP, respectively (P<0.001). The results of this study demonstrate that i-PRF increased platelet numbers by 503%, which may increase the release of growth factors. The larger zone of inhibition seen in i-PRF indicates greater antimicrobial efficacy compared to PRP and PRF, but the mechanism behind this is unknown and further research is required. This study did have limitations in that the study size was small, and there was no identification of the bacteria inhibited by the platelet preparations.

Conclusion

This review has shown the numerous potential applications of PRF in periodontology but has also highlighted its limitations and barriers to use. The exciting research being undertaken in this field seeks to negate the disadvantages of PRF and increase its accessibility to the general practitioner.

Whilst PRF was initially intended for use in oral and maxillofacial surgery[1], its applications in periodontology are widespread.

Many of the studies included in this review originated from Asia, where PRF has been widely adopted. Little literature is available with regards to why PRF has not been so widely applied in Europe, however, one can speculate it is due to the limitations described previously. However, with the development of i-PRF and other such formulations, the European field of periodontology may begin to harness the potential of platelet preparations.

On a concluding note, it is important to indicate areas that require further research. One of these areas is to investigate the exact biological mechanisms of PRF, including precisely how it exerts its effects on bone re-modelling and the immune response. The use of PRF without such knowledge is ethically questionable at best, with approval only given due to the fact it is entirely autologous. Another area where research would be beneficial is further studies to evaluate the efficacy of titanium coated tubes in the preparation of PRF, as the available literature does not define the mechanism by which it is proposed to modify the structure of PRF or provide substantial evidence that it produces any effect at all due to the small sample sizes of the studies.

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