Chapter 8

Platelet-Rich Fibrin: Utilization in the Treatment of Periodontitis

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Additional information is available at the end of the chapter

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Abstract

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the teeth and results in loss of supporting bone around the teeth leading to eventual tooth loss. It is a multifactorial disease that involves bacteria and host responses. Advanced options to treat periodontitis are aimed at regeneration procedures to restore lost periodontal structures. These include bone replacement grafts and the use of biological materials to enhance regeneration. Platelet-rich fibrin (PRF) is an autologous platelet-rich concentrate derived from a fibrin clot and is a natural source of growth factors derived from platelets, which are released over time and have been shown to have potential in periodontal procedures to enhance wound healing and regeneration. This chapter will focus on the past, current and future scope of PRF for treating periodontitis.

Keywords: platelet-rich fibrin, periodontitis, autologous, growth factors, regeneration, healing

1. Introduction

Blood is an integral part of the human body, which is responsible in delivering necessary nutrients and oxygen to different cells and also transports the metabolic waste products from those cells to be excreted out of the body. Blood includes four components: platelets, white blood cells (WBCs), red blood cells (RBCs) and plasma. Particularly, platelets play a major role in the release of growth factors at the site of injury to initiate wound healing [1]. Wound healing is an essential inflammatory process which requires cellular organization and remodeling, cellular migration and cellular proliferation. Platelets play a crucial role in all of these

functions. Due to these properties, the concept of using platelet concentrates for therapeutic purposes was introduced. The main aim was to isolate large numbers of platelets from the whole blood and then use them to enhance the wound healing process. Initially, platelet-rich plasma (PRP) was developed for this purpose and can be considered as the first generation of the platelet concentrates. Whole blood was collected and anticoagulants (i.e., calcium chloride or bovine thrombin) were added to the blood prior to centrifugation to prevent clotting. The platelet-rich fraction was removed after the blood components were separated by centrifugation. Various studies showed that the final product after processing contained 95% platelets and played direct roles in influencing osteoblasts, periodontal ligament cells, connective tissue cells and epithelial cells [2]. Due to the lengthy centrifugation protocols, the need for specialized equipment, and the need to combine the liquid PRP with other biomaterials made it cumbersome to use in a clinical setting for outpatient oral and maxillofacial surgeries and periodontal surgical procedures. To overcome the limitations presented by PRP, the second generation of platelet concentrates (i.e., platelet-rich fibrin, PRF) was developed [3].

With the main objective of obtaining platelet concentrates without the addition of the anticoagulation agents, a new protocol was developed which included centrifuging the blood at high speed (3000 rpm) for 10 minutes to separate different components that included the heavier RBCs in the bottom of the centrifugation tube, clear serum at the top of the tube with an interposed fibrin clot layer consisting largely of platelets and WBCs [3, 4]. Because no anti-coagulation factors were used, a three-dimensional yellow fibrin clot was obtained between the two liquid layers and was termed as PRF (**Figure 1**). It was shown that approximately 97% of the platelets and >50% of the leucocytes in the blood sample were concentrated in the PRF clot and due to its additional

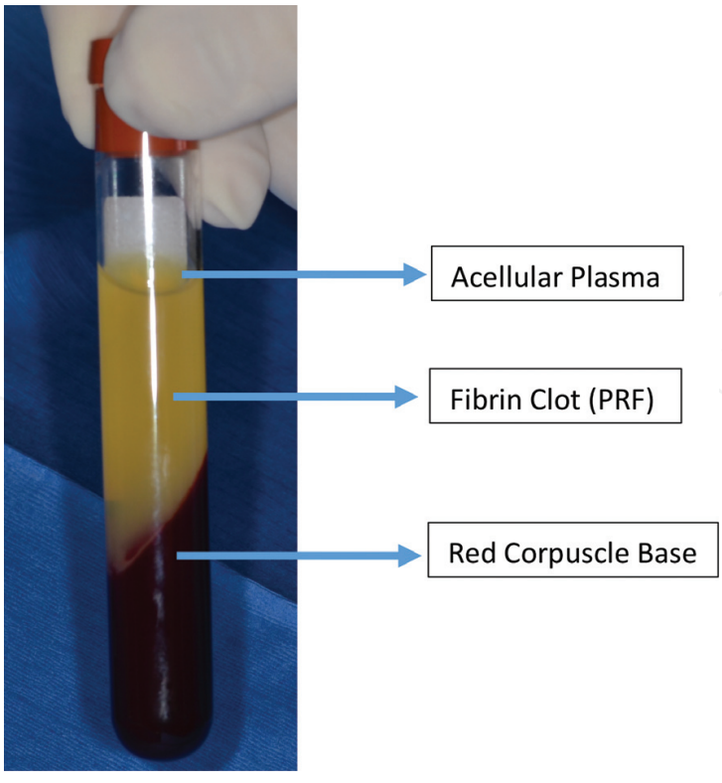

Figure 1. PRF clot after centrifugation.

leucocyte content, these platelet concentrates are also sometimes referred to as leucocyte-PRF (L-PRF) [4].

1.1. PRF processing

Intravenous blood is collected through venipuncture (superficial veins in arm: median cubital vein, cephalic vein, basilica vein or dorsal metacarpal veins) and collected in 10-ml sterile tubes without anticoagulants (**Figure 2a**). The volume of blood depends upon the application of the PRF. Immediately after collection of the venous blood, the tubes are centrifuged at specified speed and time as shown in **Figure 2b**. This centrifugation allows the formation of the fibrin-scaffold in the middle of the tube as shown in **Figures 1** and **2c**. This fibrin clot is separated from the red corpuscles base with the help of the sterile tweezers and scissors and is transferred to the sterile PRF box for compression (**Figure 2d**). The minimum compression period required is 4–5 minutes for uniform thickness. This converts the clot into PRF membrane (**Figure 2e**) which can be used for various applications in the field of periodontics as discussed later. The lower chamber of the box collects the exudate after the compression which may be used for hydration of other regenerative materials (**Figure 2f**).

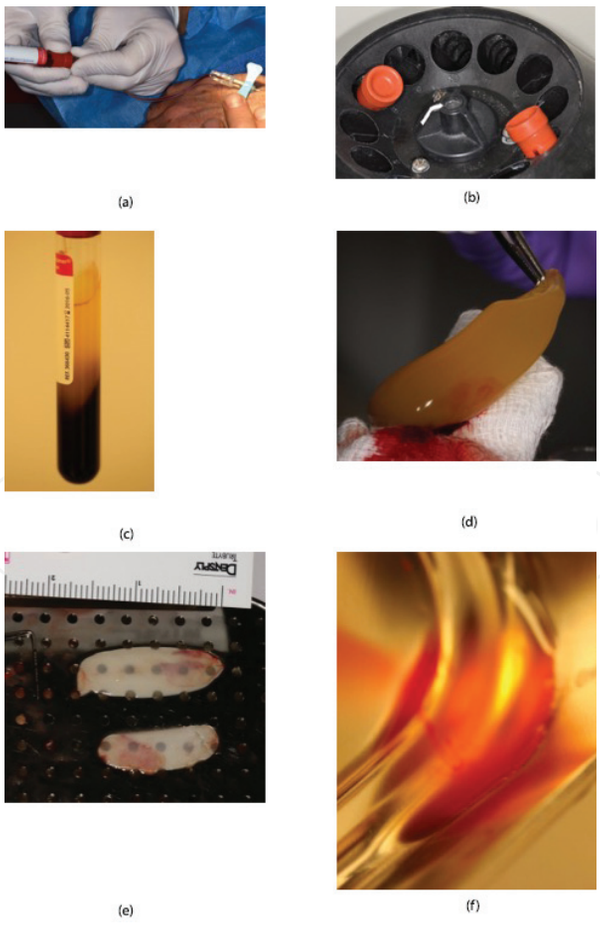

Figure 2. (a–f) PRF procedure. (a) Blood collection, (b) centrifugation, (c and d) fibrin clot, (e) PRF membrane after compression, (f) Exudate collected in lower chamber.

1.2. Properties of PRF

With the advancement and research to explore the properties of the PRF, various procedures have been established for the formulation of the PRF [5]. Studies have been carried out to evaluate the significance of different protocols which are based on different centrifugation speeds and times [5, 6]. The L-PRF procedure includes centrifugation at 2700 rpm for 12 minutes was the first well-documented procedure. It was followed by an advanced-PRF (A-PRF) procedure, which includes centrifugation at 1500 rpm for 14 minutes [5–7]. The differences in the properties due to different procedures will be discussed based on the available evidence. All three concentrates of platelets (PRP, L-PRF, and A-PRF) have been shown to release growth factors when processed as described above but each differs in its growth factor release kinetics [6]. PRFs, the most commonly studied platelet concentrate, have been shown to contain growth factors that are produced by and released from platelets including: platelet-derived growth factors (PDGFs), transforming growth factor β1 (TGF-β1), vascular endothelial growth factor (VEGF), endothelial growth factor (EGF) and insulin-like growth factors (IGFs). These are slowly released over a period of time, which may extend up to 28 days when PRF is used as the membrane to cover a periodontal defect [3, 6]. The primary functions of each growth factor are discussed in **Table 1**.

Growth factor	Functions
Platelet-derived growth factors (PDGFs)	Specific roles include proliferation of cells, cellular migration and collagen production for remodeling of extra-cellular matrix to repair the wound.
Transforming growth factor β1 (TGF-β1)	Tissue repair, extracellular matrix synthesis and immune modulation. Specific roles played by TGF-β1 includes angiogenesis, re-epithelization and regeneration of connective tissue. Due to bone morphogenetic proteins (BMPs) being part of TGF family. They also play role in bone formation.
Vascular endothelial growth factor (VEGF)	Primary function is angiogenesis. Also, plays a role in tissue remodeling.
Endothelial growth factor (EGF)	Proliferation and multiplication of endothelial and mesenchymal cells, which leads to epithelization.
Insulin-like growth factors (IGFs)	Cell-protective in nature and participates in proliferation and differentiation of a variety of cells.

Table 1. Growth factors found in PRF and their functions.

The most important aspect of PRF is growth factor release, which is why PRFs are being used as a material to promote healing and regeneration of tissues. Information about the number of growth factors released over time will aid in understanding the roles played by PRF in tissue repair. The most comprehensive research in this regard was done by Kobayashi and co-workers [6]. They evaluated the growth factor release from PRP, L-PRF, and A-PRF over a period of 10 days and found that L-PRFs and A-PRFs released significantly higher amounts of growth factors compared to PRPs. PDGF, VEGF, IGF, EGF, and TGF-β1 were evaluated in this study [6]. The same study showed that A-PRF had significantly more growth factor at 1, 3 or 10 days when compared to L-PRF. This study demonstrated that second-generation PRFs were superior over first-generation PRP with respect to the number of growth factors released and A-PRF (low centrifugation concept) can enhance the level of growth factors entrapped in the fibrin clot.

To understand the roles of PRFs in the wound healing process, it is important to understand the biological properties of PRFs. It is important to study how the fibrin network releases growth factors over time leading to enhanced cell migration and proliferation, and thus cell maturation. The periodontium is a unique complex structure of soft and hard tissues consisting of gingival connective tissue, periodontal ligament tissue, cementum and bone that tends to repair and heal by collagenous fibrous tissue reformation and maturation. One of the important factors responsible for regeneration of the periodontal structures involves periodontal ligament cells. Periodontal ligament cells primarily consist of periodontal ligament fibroblasts, which play a key role in the maintenance of periodontal health as they are responsible for formation and remodeling of alveolar bone in the development of periodontitis [8]. Also, studies have found that human periodontal ligament fibroblasts (HPLFs) form a heterogeneous population, whereas some cells exhibit phenotypic characteristics of osteoblast-like cells which might have the potential to further differentiate to osteoprogenitor cells leading to osteoblasts or cementoblasts [8]. Another important cell type which aids in the maintenance of the periodontal structures along with HPLFs is human gingival fibroblasts (HGFs), which are abundantly present in the gingival tissue and support the periodontal tissues. It is important to understand how PRF biologically affects both HPLF and HGF. Chang and co-workers [9] investigated the effects of PRF from healthy individuals on HPLF. They measured the expression of phosphorylated extracellular signal-regulated protein kinase (p-ERK), osteoprotegerin (OPG) and alkaline phosphatase (ALP) activity. This study showed that PRF significantly increased ERK phosphorylation and OPG in HPLF in a time-dependent manner, along with upregulated ALP activity. This demonstrated that PRF may provide benefits for periodontal tissue regeneration. Another study by Vahabi et al. [10] showed that PRF when cultured along with HGF for a period of 24, 48 or 72 hours and evaluated through a methyl thiazol tetrazolium assay led to statistically significant proliferation of HGF at 24 hours, but no proliferation of HGF was observed at 48 and 72 hours along with the viability of the cells also decreasing with time. The explanation for proliferation seen up to 24 hours could co-relate with the maximum number of HGF being reached per available area. More recently, Fujioka-Kobayashi et al. [11] compared L-PRF and A-PRF with regards to their effects on HGF proliferation and viability. They used the same assay as mentioned in the Vahabi study [10] to measure proliferation, but additionally, they performed real-time PCR analysis where RNA was harvested from HGF samples to assess RNA levels of PDGF, TGF-beta, and collagen type I. This study demonstrated a 200% increase in the proliferation of HGF when combined with PRF at 24 hours and increased cellular proliferation was noted with increased numbers of cells at 3 and 5 days. A significant increase in growth factor levels was seen in the culture when combined with PRF. All of this data supports that PRFs can play a significant role in the healing and regeneration of periodontal structures when used as biological modifier during periodontal and oral-maxillofacial surgeries.

2. Applications of PRF: an overview

A true regenerative procedure in periodontology includes regeneration of both soft tissues (periodontal ligament) and mineralized tissues (cementum and alveolar bone) [12, 13].

Guided tissue regeneration (GTR) procedures are advocated for regeneration of periodontal defects and involve the use of barrier membranes which prevents the downgrowth of the epithelium and excludes gingival connective from the healing wound to allow selective cell repopulation from the periodontal ligament in alveolar bone. The barrier membranes can be bioresorbable (made of collagen material) or non-bioresorbable (made of polytetrafluoroethylene material) and studies have shown that resorbable membranes show comparable results with fewer post-surgical complications for GTR procedures when compared to non-resorbable membranes [12, 14]. Some periodontal regenerative techniques include using bone replacement grafts like demineralized freeze-dried bone allograft or biological modifiers (i.e. enamel matrix derivative and recombinant human platelet-derived growth factor-BB) [15–17]. These commercially available growth modifiers have been shown to have significant roles in stimulating wound healing and tissue regeneration [12]. PRFs can be used as a potential barrier membrane with enhanced wound healing properties due to its rich growth factors content [7]. PRF membranes can be used as an adjunct in the future implant site preparation [18, 19]. Subepithelial connective tissue grafts (SCTGs) are considered to be the gold standard for root coverage procedures but involve a second surgical site in the oral cavity to harvest the graft [20, 21]. The use of PRF for root coverage procedures has been shown to be an alternative to the SCTG for root coverage procedures with reduced patient post-surgical discomfort [22, 23].

2.1. Management of extraction sockets with PRF

Following tooth extraction, alveolar bone dimensions are reduced both in vertical and horizontal dimensions as part of the normal healing process [24]. Various treatment interventions have been carried out to reduce changes in post-extraction alveolar ridge dimensions either for esthetic purposes or for future implant placement [25]. Treatment options which include use of allograft or xenograft bone graft materials with or without barrier membranes have shown positive results in preventing alveolar ridge collapse when compared to sites without any intervention [25]. Considering the beneficial properties of the PRF, it has been used as an adjunct in socket grafting procedures with or without bone graft material to improve the healing and maintenance of the alveolar ridge dimensions [18, 26]. Groups treated with the PRF showed better results when compared to the non-grafted control groups with respect to vertical and horizontal dimensions of the alveolar ridge with less discomfort and better clinical and histological healing pattern in the socket [18, 26, 27]. **Figure 3** shows a clinical case of a patient with a non-restorable molar seeking future implant placement. The tooth was extracted and the socket was filled with allograft bone particles and covered with a PRF membrane. Healing at 1 week (**Figure 3d**) demonstrated enhanced soft tissue healing over the socket with no reported patient discomfort.

2.2. Guided bone regeneration (GBR) with PRF

Edentulism for long periods or following trauma can cause ridge deficiencies that are not suitable for implant placement. GBR procedures using barrier membranes and bone grafts

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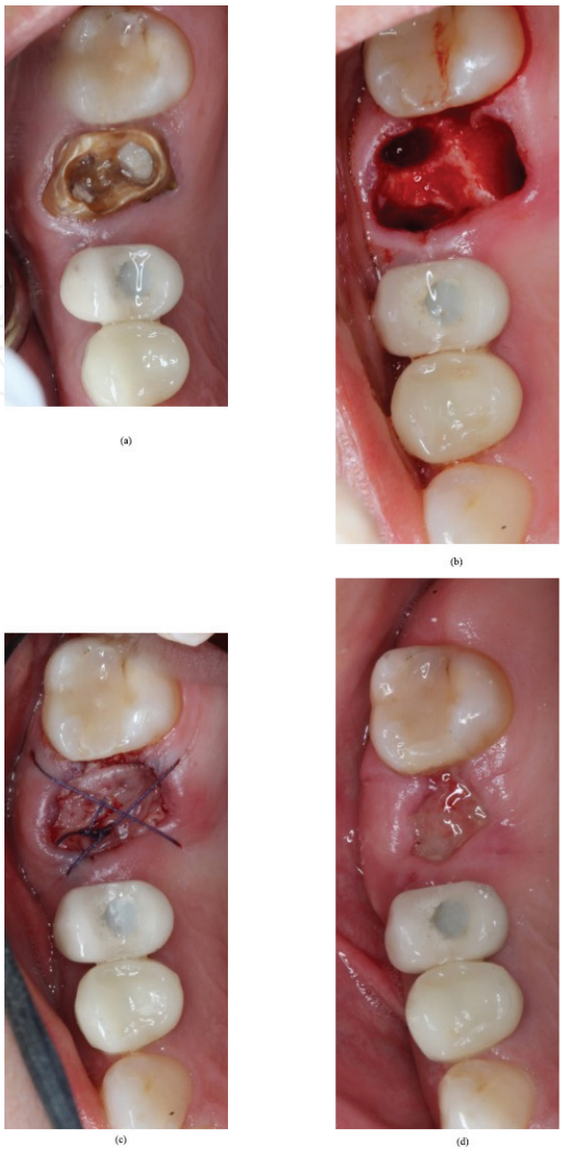

Figure 3. Management of extraction socket and site preparation for future implant placement. (a) Hopeless #30 to be replaced with dental implant, (b) Atraumatic surgical extraction, (c) allograft bone graft placed in the socket for space maintenance and covered with PRF membrane, (d) healing at 1 week with visible PRF membrane.

bone regeneration have shown good clinical outcomes [28, 29] and successful long-term results with implants placed in the regenerated bone [30]. Based on the defect size and the required amount of bone to be regenerated, a decision tree is available in the literature which helps the clinician to decide on the GBR technique [31]. Although GBR procedures for horizontal bone augmentation have shown predictable results, there are multiple reported complications associated with such procedures which can lead to poor or failed treatment outcomes [32]. The most common wound healing complication reported is membrane exposure which can eventually lead to treatment failure or infection [32]. The membrane exposures can happen either due to the insufficient blood supply to the flaps leading to necrosis or due to the inability of achieving and maintaining passive primary closure of the flaps [32]. PRF can be used as an

adjunct in such procedures to enhance healing and regeneration [7, 19, 27]. The patient illustrated below (**Figure 4**) presented with insufficient bone dimensions for implant placement and underwent a GBR procedure with PRF as an adjunct with resultant good healing without any reported discomfort.

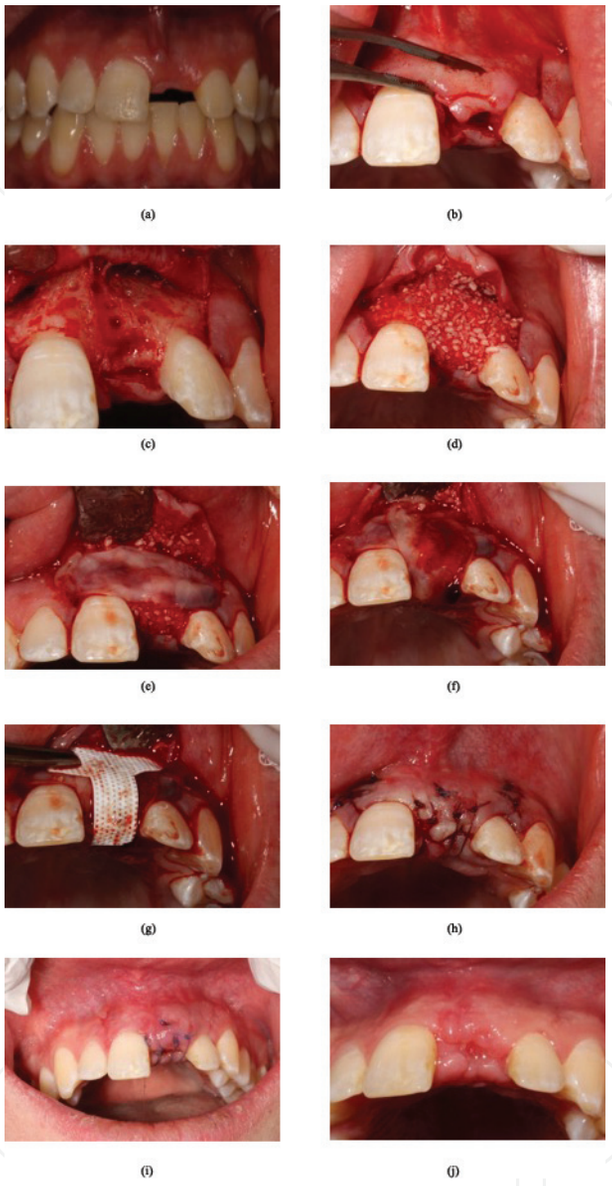

Figure 4. GBR at site #9 for future implant placement. (a) #9 Edentulous site with insufficient bone for implant placement, (b) incisions, (c) defect with decortications, (d) particulate bone allograft to fill the defect, (e) PRF membrane placed horizontally over the bone graft. (f) Second PRF membrane placed vertically, (g) titanium-reinforced d-PTFE membrane for space maintenance placed over the PRF membrane, (h) primary closure achieved, (i) healing at 1 week, (j) healing at 4-months after titanium-reinforced d-PTFE membrane removal.

2.3. PRF used in sinus procedures

The edentulous posterior maxilla can be a challenging site to restore with implants due to alveolar ridge resorption and the presence of maxillary sinus pneumatization which tends to increase over time. Sinus augmentation procedures are the treatment of choice to restore

posterior maxilla with deficient bone height due to sinus pneumatization [33]. The two most common sinus augmentation procedures include the osteotome sinus augmentation and lateral window sinus augmentation with a common goal of increasing vertical bone dimensions. Both the procedures have shown high long-term implant survival rates following sinus augmentation [33]. Due to the healing and regenerative properties of PRF, it has been incorporated into sinus procedures: as a sole grafting material, in combination with allograft and xenograft material, as a membrane to cover the graft material, and to repair intra-operative Schneiderian membrane perforations [34–36]. PRF when used either as a sole grafting material or in combination with other materials have shown positive and promising results with respect to faster healing and maturation of bone [35]. The case demonstrated below (**Figure 5**) shows the use of

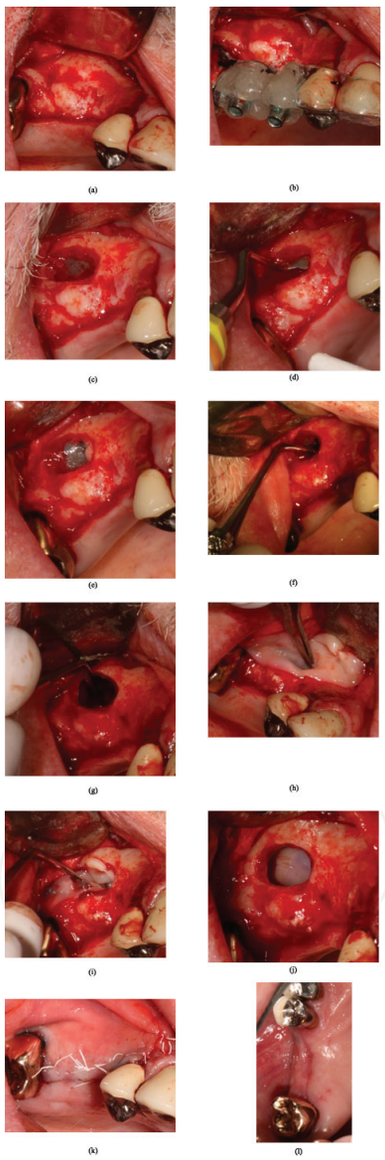

Figure 5. Lateral window sinus augmentation procedure to place implants at #3 and 4, due to insufficient vertical height. (a) Full thickness mucoperiosteal flap reflection, (b) surgical guide at place to guide lateral window position, (c) lateral window ostectomy created, (d) sinus elevator used to elevate Schneiderian membrane, (e) intact Schneiderian membrane, (f) accidental Schneiderian membrane perforation, (g) Schneiderian membrane perforation, (h) PRF membrane used to repair Schneiderian membrane, (i) second PRF membrane to provide stability and maintaining integrity of the perforated Schneiderian membrane, (j) Schneiderian membrane repaired, (k) primary closure achieved, (l) healing at 2-weeks.

PRF to reconstruct a Schneiderian membrane perforation, the most common intra-operative complication of the lateral window sinus augmentation technique [37].

2.4. Root coverage procedure with PRF

Another aspect of the periodontal therapy is the treatment of mucogingival defects which refers to gingival recession leading to root exposure. Gingival recession and root exposure can lead to sensitivity and esthetic concerns for the patient. A systematic review has shown predictable results with root coverage procedures for Miller Class I and Class II defects [21]. The most predictable results have been shown when SCTG is used as a material for root coverage procedure along with the coronal advancement of the flaps [21]. For harvesting connective tissue graft, a second surgical site (i.e. palate or tuberosity region) is needed in the oral cavity which leads to increased patient discomfort. Clinical studies have shown similar results to SCTG when PRF is used as a material for root coverage procedures [22, 23]. **Figure 6** shows a successful root

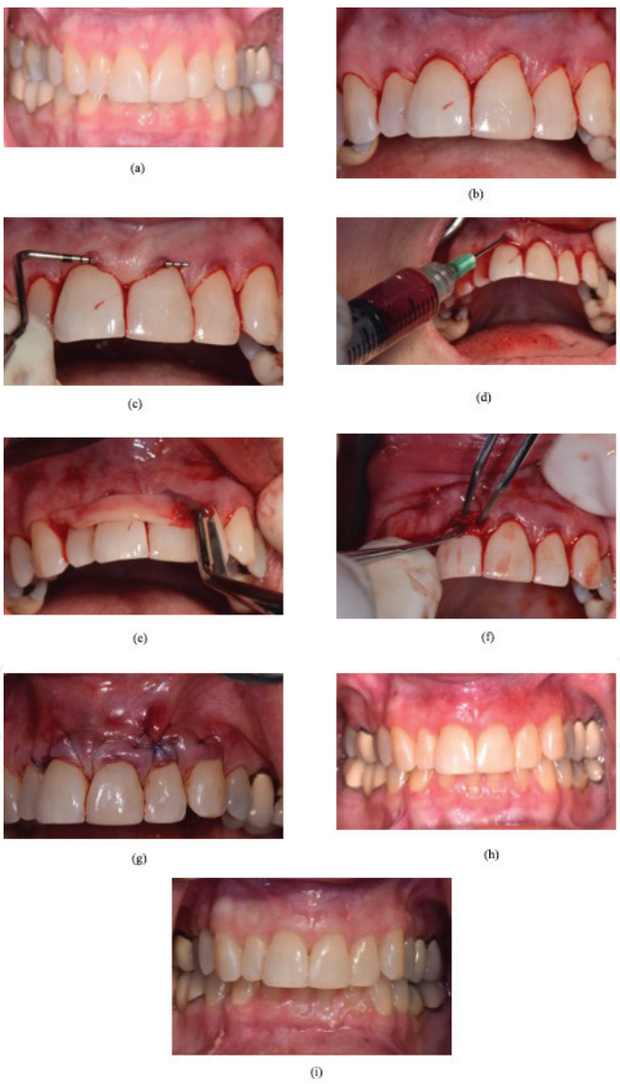

Figure 6. Root coverage procedure for #7–11. (a) Gingival recession shown from #7–11, (b, c) tunnel preparation shown for PRF placement, (d) Exudate collected after fibrin clot compression used to irrigate the site, (e) PRF membrane shown over the site, (f) PRF membrane placed in the tunnel, (g) soft tissue is coronally advanced with the help of sutures, (h) healing at 2 weeks, (i) stable root coverage at 3 months.

coverage procedure when PRF is tunneled and flap is coronally advanced. Healing and root coverage is stable at 3 months (**Figure 6i**).

3. Future scope and conclusion

The current research on PRF focuses on the clinical applications of the PRF in periodontology and implant dentistry and has shown promising results with better healing outcomes and less patient discomfort. At the same time, there is need to evaluate the properties of PRF which includes quantification of growth factors and the number of growth factors released from PRF over time. It is important to study the variables including age, sex, and the influence of any systemic disease on PRF quality. Further research is also needed on different formulation of the platelet concentrates to make it optimize its use for different procedures.

Overall, PRF can be utilized for many periodontal and implant procedures capitalizing on taking advantage of considering (1) the use of an autologous source, (2) enhanced healing and regeneration potential, and (3) a less expensive alternative to other commercially available biological modifiers.

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