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The Role of Platelet Rich Fibrin for Closure of Oronasal Fistula Post Palatoplasty through Abilities to Keep Growth Factor Activity for a Relatively Longer Period and Stimulate Tissue Regeneration Effectively

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ABSTRACT

Oronasal fistula is one of the unfortunate consequences of cleft palate surgery. This can be done after palate surgery in patients with cleft palate, defined as an abnormal connection between the oral and nasal cavities. Multiple systems have attempted that classification. It can be a small, symptomatic or asymptomatic fistula that needs correction. Its speed varies greatly depending on many factors. Both surgical and non-surgical methods (the advantages and disadvantages of each should be considered) are available for correction, and there are combination therapies that help improve surgical outcomes. Platelet-rich fibrin (PRF) is a novel Generation platelet concentrate, very easy to prepare and handle without the use of biochemicals. Its production is dependent on the accumulation of platelets that release cytokines and growth factors. Enriched with growth factors, this hemostatic plug is easy to prepare and operate. Adapted for soft and hard tissue healing. It is used in various fields of dentistry, especially oral and maxillofacial surgery. Reports on the role of PRF in repairing oronasal fistula closure are sparse in the literature, especially in relation to other soft tissue flaps.

KEYWORDS: Platelet Rich Fibrin, Oronasal Fistula, Palatoplasty, Tissue Regeneration

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INTRODUCTION

Cleft lip and palate (CLP) is one of the most common birth defects. It is a multifactorial disorder involving other factors, including radiation, maternal hypoxia, teratogens, nutritional deficiencies, and chemical exposure. Pathological consequences of cleft palate include feeding and nutrition disorders, recurrent ear infections, hearing impairment, abnormal language development, and distortion of facial growth. One of the challenging problems in wound healing that occur after surgical repair of cleft palate is cleft recurrence or fistula development.[1]

In general, fistula refers to a communicating track between two epithelial surfaces, commonly between a hollow viscus and the skin (external fistula) or between two hollow viscera (internal fistula), lined with granulation tissue which is subsequently epithelized. Specifically, the nasal cavity is separated from the oral cavity anteriorly by the premaxilla and maxilla and posteriorly by the horizontal plate of the palatine bone. The oronasal fistula (ONF) is an internal fistula and represents an abnormal epithelized track communicating between the nasal cavity and mouth.[2]

Although there are many causes of oronasal fistula, congenital causes (primary fistula) in patients with cleft palate remain the main cause of oronasal fistula. Causes of fistula (secondary fistula) after palatoplasty surgery can be caused by any of the following factors [3-4]:

1. Causes related to the nature of the cleft, Example the width of the cleft.
2. Extent of palatal segment loss and cleft palate segment misalignment and distortion.
3. Causes related to the procedure example post-operative bleeding, inadequate flap dissection, closure under tension, hematoma formation between the oral and nasal layers, and infection.
4. Patient-related causes.

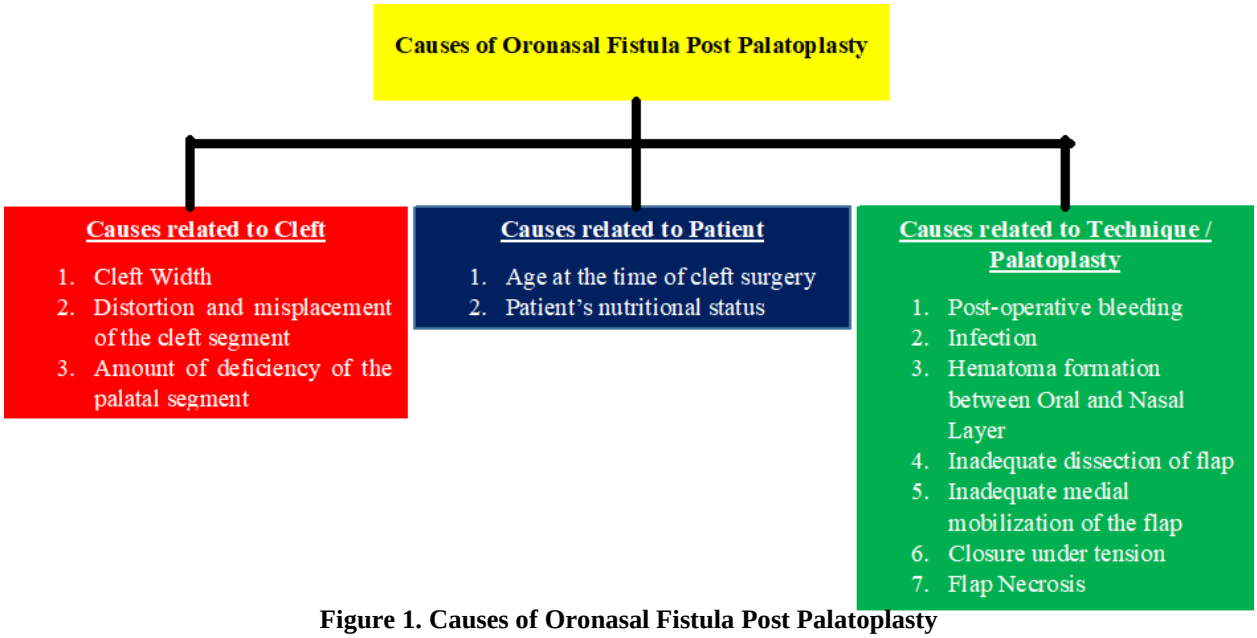

Figure 1. Causes of Oronasal Fistula Post Palatoplasty

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate and is used as a bone graft material for periodontal regeneration, ridge augmentation, sinus lift procedures for implant placement, and to cover recession defects in the form of membranes and treatment of extraction sockets.[5] The use of PRF in palatoplasty exploits its ability to form a three-dimensional fibrin matrix that serves as a scaffold for tissue regeneration and sustained release of growth factors involved in wound healing without activating an inflammatory response. And this is a great advantage in wound healing process. PRF has the ability to strengthen soft tissue, ensuring optimal wound healing and making wound breakdown difficult. This makes PRF a reliable peripheral blood extract that extracts growth factors from the patient's own blood without the use of additives.[6]

Role of Platelet Rich Fibrin in Tissue Regeneration Process

Platelet-Rich Fibrin, a new generation platelet concentrate that boosts the healing process for maximum predictability. It is composed of platelets, cytokines and a fibrin matrix. Platelet and leukocyte cytokines play an important role in the biology of this biomaterial. Platelet degranulation involves the release of cytokines that can stimulate cell migration and proliferation within the fibrin matrix, initiating the initial healing phase.[7] The fibrin matrix that supports it represents a crucial element responsible for the true therapeutic potential of PRF. The biological activity of the fibrin molecule highlights its important ability to form scars. However, a detailed understanding of the components of PRF and their biological roles will help us understand this biomaterial from a clinical perspective and subsequently expand the area of therapeutic applications.[8-9]

Fibrin is the active form of the fibrinogen molecule present in both plasma and platelet granules. Plays an important role in achieving platelet aggregation and hemostasis. Soluble fibrinogen is converted to insoluble fibrin, which polymerizes into the cicatricial matrix. The slow and natural polymerization of fibrin results in its homogenous 3-dimensional organization during the centrifugation performed in PRF preparation. This leads to the intrinsic incorporation of platelet cytokines and glycan chains in the fibrin meshes. The fibrin matrix present in PRF is flexible, elastic and extremely strong. Since it has a low concentration of thrombin, an equilateral transition occurs. These connected junctions allow the withdrawal of fine and flexible fibrin networks that can support cytokines and cell migration that occurs. Since the release and use of these cytokines occurs during the initial remodeling of the scar matrix, this leads to increased longevity of these cytokines.[9]

Cytokines are therefore available for the requisite period necessary for cells to initiate healing. The fibrin network of PRF is different from that of PRP. In PRP, there are bidirectional connections that result in a rigid network that does not consider cytokine tangles or cell migration. The increased thrombin required for rapid curing of PRP results in a rigid polymerized material.[10-11]

A. **Effect of fibrin on bone tissue.** There is a significant lack of documentation on the direct interaction between fibrin and bone tissue. However, osteogenic proteins embedded in fibrin matrices have the ability to be consistently released, emphasizing angiogenic, hemostatic, and osteoconductive properties. Fibrin is certified as a support matrix for BMP. BMPs embedded in fibrin are gradually released and can induce bone formation. Consistent release of VEGF, FGF, and PDGF aids angiogenesis. Hemostasis is achieved by the fibrin clot's ability to remove circulating stem cells, allowing vascular and tissue repair.[12]

B. Effect of Fibrin on Mesenchymal Stem Cells. Fibrin matrix acts as a scaffold for undifferentiated mesenchymal cells, promoting their differentiation and assisting tissue regeneration.[13]

C. Effect of Fibrin in Angiogenesis. When cytokines are trapped in the three-dimensional structure of the fibrin matrix, they are released in a sustained manner. This is very important for the initiation of angiogenesis. Cytokines responsible for this effect include her FGF, VEGF, angiopoietin, and PDGF in fibrin gels. Fibrin matrix stiffness plays an important role in the process of angiogenesis in response to FGF and VEGF stimulation. Increased expression of the $\alpha v\beta 3$ integrin in response to fibrin enables endothelial cells to bind fibrin itself, fibronectin, and vitronectin.[14]

D. Fibrin Assisted Immune Response. Up-regulation of CD11c/CD18 receptors on endothelial cells by fibrin promotes increased adhesion to endothelial cells and fibrinogen and migration of neutrophils. Fibrin and fibronectin also regulate wound colonization by macrophages.[15]

Platelets, as a major component of PRF, represent the primary cells responsible for PRF's biological activity. These cells play an important role in blood clot formation, but contain various platelet-derived protein molecules involved in the wound-healing signaling cascade. All these substances are stored by three types of granules (alpha, delta and lambda) contained in platelets. Alpha granules are the major reservoir of growth factors and the most abundant platelet granules. These granules contain various growth factors involved in soft and hard tissue regeneration after injury and are released by exocytosis upon platelet activation. Major growth factors in PRF include transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). Furthermore, among the growth factors released from platelets, PRF contains immune cytokines such as interleukin (IL)-1β, IL-6, IL-4, and tumor necrosis factor (TNF)-α.[11]

Table 1. Growth factors and cytokines present in PRF

Growth factors and cytokines present in PRF	Function
Transforming growth factor-β (TGF-β)	Stimulates angiogenesis, fibronectin, and collagen production; prevents collagen breakdown; induces fibroblast and immune cells chemotaxis; inhibits osteoclast formation and bone degeneration
Platelet-derived growth factor (PDGF)	Provokes migration and proliferation of mesenchymatous cell lineage; enables angiogenesis, macrophages chemotaxis, and activation; induces TGF-β secretion from macrophages
Insulin growth factor-1 (IGF-1)	Stimulates chemotaxis and activation of osteoblasts and bone formation; induces differentiation and mitogenesis of mesenchymal cells
Vascular endothelial growth factor (VEGF)	Initiates angiogenesis; enhances permeability of the vessels; induces endothelial cell proliferation and migration
Epidermal growth factor (EGF)	Promotes angiogenesis; stimulates proliferation and differentiation of epithelial cells; increases cytokine secretion in epithelial and mesenchymal cells
Interleukin-1β (IL-1β)	Increases expression of adhesive molecules on endothelial cells; stimulates helper T cell, chemotaxis of lymphocytes; activates osteoblasts
Interleukin-6 (IL-6)	Stimulates B-cell differentiation and antibody secretion; induces differentiation of naive T cells in cytotoxic T lymphocytes
Tumor necrosis factor-α (TNF-α)	Induces neutrophil cytotoxicity; stimulates cell survival and proliferation; enhances the remodeling capacities of fibroblasts
Interleukin-4 (IL-4)	Induces B-cell differentiation into plasmocytes, B-cell class switching to IgE, differentiation of naive helper T cells in Th2 cells

Studies have shown that along with high levels of platelets and released growth factors, PRF is rich in leukocytes and immune cytokines, including IL-1β, IL-4, IL-6, and TNF-α. Such a phenomenon represents high scientific value, as leukocytes are major drivers of bone and soft tissue regeneration by releasing lymphogenic factors responsible for cell crosstalk in tissue regeneration. Consistent with these results, a recent study showed that reducing the relative centrifugal force significantly increased the total number of platelets and leukocytes and the abundance of growth factors. This suggests that the low-speed centrifugation concept leads to increased regenerative capacity of PRF. Fibrin and fibrin degradation products stimulate neutrophil migration, activation and release of neutrophil proteases. These neutrophils eliminate contaminating bacteria at the wound site by generating oxygen radicals and enzymatic digestion. Furthermore, the interaction of fibrin with monocytes and macrophages regulates phagocytosis, indicating that macrophages play a central role in the transition between wound inflammation and wound healing. Without leukocytes, precise cell-to-cell communication for tissue regeneration is not possible, suggesting that platelets are not only involved in tissue regeneration, but also require leukocytes to function in the tissue regeneration process.[10-11]

Platelet Rich Fibrin Keep Growth Factor Activity for Longer Period

Most notably, compared to the rapid growth factor release of PRP, PRF releases growth factors for up to 7 days for most growth factors and even longer for others. The composition of PRF has been suggested to help prevent rapid proteolysis of growth factors and enable prolonged secretion. Furthermore, the slow polymerization and remodeling of the fibrin matrix in PRF effectively protects growth factors and other vital cells compared to the fast and random polymerization of PRP.[16] Masuki et al. concluded from a comparative analysis that growth factor concentrations were generally higher in PRF than in PRP.[11] This is a finding that supports the remarkable potency of PRF in stimulating angiogenesis, wound healing, and tissue regeneration. As mentioned above, growth factors chemotactically attract mesenchymal cells. It is therefore reasonable to hypothesize that the sustained growth factor secretion of PRF induces more migration of mesenchymal cells compared with PRP.[16]

Table 2. Advantages and Shortcoming of Platelet Rich Fibrin

Advantages of PRF	Shortcomings of PRF
Formulation of a PRF membrane that possesses elasticity and flexibility No use of anticoagulants Slow natural polymerization 3D fibrin network forming a matrix aiding in cytokine retention for extended periods It is inexpensive and involves simple procedure that requires only one centrifugation step	Rapid use of the PRF without delay or short handling time Storage of PRF membrane is not possible due to potential bacterial contamination and dehydration Low quantity of PRF is obtained

Platelet Rich Fibrin Preparation

The preparation of PRF requires approximately 10 ml of venous blood in a sterile 10 cm plastic syringe. Under sterile conditions, the collected blood was immediately transferred to plain 10 ml tubes without added anticoagulant. The centrifuge was set at 3000 rpm and the spin time was 10 minutes to generate PRP until 3 layers were obtained. The top layer is composed of platelet-poor plasma, the middle layer contains PRF, and the bottom layer contains red blood cells. The isolated PRF is collected using sterile buffer and formed until membranes are obtained.[17]

Platelet Rich Fibrin Application for Oronasal Fistula Post Palatoplasty

The optimal goals for repairing a cleft palate are satisfactory anatomical and functional closure of the defect, normal speech, no reflux of fluids or food into the nasal passages limitation of maxillary growth disturbance, and minimizing the potential for hearing loss. Many materials have been used as scaffolds for tissue engineering: Hyaluronic acid, hydroxyapatite, PRP, and PRF. They stimulate bone regeneration from undifferentiated mesenchymal cells. Diverse other synthetic materials have also been used in palatal repair as intervening grafts such as alloderm and collagen membranes.[17]

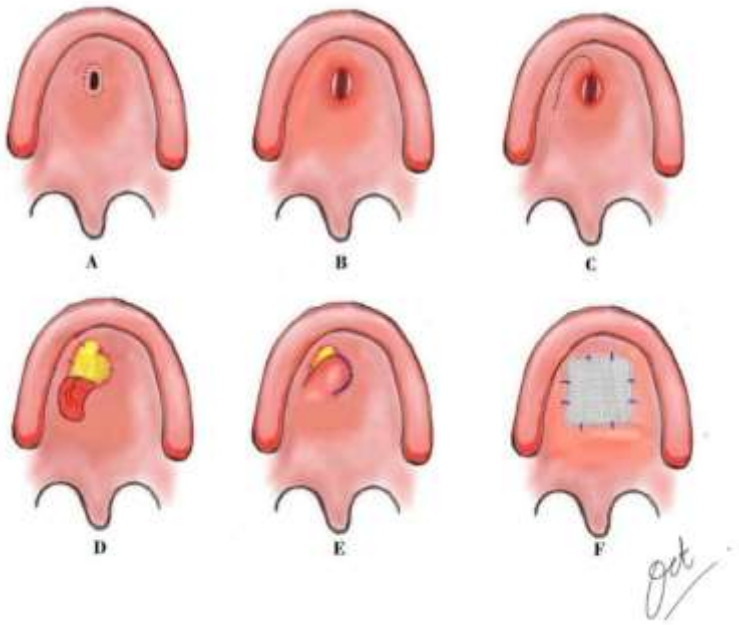

Figure 2. Closure of Oronasal Fistula with Rotational Flap and Platelet Rich Fibrin (Author's Illustration). (A) Outline of the incision for the turn over flap for creating the nasal floor; (B) Nasal layer closure complete with Turn Over Flap; (C) Design of a rotation flap from the Palatal Mucosa for oral layer closure; (D) The Platelet Rich Fibrin placed over the already reconstructed nasal layer with the size is approximately equal to the flap previously design and secure with sutures; (E) The final repair; (F) Vaseline gauze placement over the flap – PRF and anchored with sutures.[19,21,22]

A study used a local mucoperiosteal flap supplemented with PRF gel mixed with autogenous bone graft and placed between two solid collagen sheets that bridged the bone defect between the palate and nasal mucosa in 11 recurrences. Complete palatal fistula closure was achieved in 90.9% (6–24 months follow-up), with a reduced incidence of recurrence reported by other authors with other techniques.[18] A study by Taiwo et al. also reported their case used of PRF in patient with palatal fistula which was successfully managed. The palate was anesthetized using 2% lignocaine HCl and bleeding from the surrounding tissue was induced at the palatal perforation site. A layer of PRF was placed in the perforation after raising the palatal mucoperiosteum flap and secured with sutures. Place petrolatum gauze over the PRF and secure with sutures. Post-operative care: Arm restrains were fixed to the patient's body to inhibit trauma of the wound by the child's fingers. Patient's feeding was done only through plastic syringe, breast or bottle feeding were inhibited to avoid trauma by suction at first week.[17] Three days after PRF application, the petroleum jelly gauze was removed and the site was evaluated. A clinical examination of the wound site showed that the sutures were intact and the PRF was attached to the palatal mucosa. A 7-day postoperative review showed complete epithelialization and complete wound closure. The patient was followed for 1 year, during which time no evidence of fistula repair disruption was observed.[19] Platelet-rich fibrin (PRF) has also been investigated as a scaffold for human osteoblast carriers. The metabolic activity and proliferation of human osteoblasts were greatly supported by PRF membranes.[20]

CONCLUSION

The application of autologous platelet-rich fibrin could present new possibilities for enhanced healing and functional recovery. The use of PRF as a graft is easy, does not require donor site morbidity or deformity. It is safe and effective in the closure of ONF post palatoplasty.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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