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The Use of Platelet-rich Fibrin (PRF) in Cleft Lip and Palate Patients: A Review Article.

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Abstract

The purpose of this review article is to introduce the large number of PRF-related studies that have been published to date in the dental industry to better comprehend the clinical processes where Platelet-rich Fibrin may be used to promote bone and tissue growth as it has been shown that Platelet-rich Fibrin increases platelet and fibrin concentration when placed which in turn will eventually speed up the rate of bone development in grafts and enhance the density of the bone created in the region of cleft palate. According to some, the high concentration of platelets, which contain a range of growth factors, is what causes these biomaterials' effects. In addition, the review will highlight the history of evolution, classification, and protocols for platelet-rich fibrin production. Finally, the application of platelet-rich fibrin in cleft lip and palate patients will be reviewed.

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استخدام الفيبرين الغنى بالصفائح الدموية (PRF) فى العظام السنخية فى مرضى الشفة المشقوقة والحنك (مقالة مراجعة)

الملخص

الغرض من مقال المراجعة هذا هو تقديم عدد كبير من الدراسات المتعلقة بـ PRF والتي تم نشرها حتى الآن في صناعة طب الأسنان لفهم العمليات السريرية بشكل أفضل حيث يمكن استخدام الفيبرين الغني بالصفائح الدموية لتعزيز نمو العظام والأنسجة. تأثير الفيبرين الغني بالصفائح الدموية على زيادة تركيز الصفائح الدموية والفيبرين عند وضعها ومن أجل أن يدرس الباحثون إمكانية قيام الفيبرين الغني بالصفائح الدموية بتسريع معدل نمو العظام في الطعوم وتعزيز كثافة العظم المتكون في المنطقة من الحنك المشقوق. ووفقا للبعض، فإن التركيز العالي للصفائح الدموية، التي تحتوي على مجموعة من عوامل النمو، هو ما يسبب تأثيرات هذه المواد الحيوية. هناك أيضًا بروتوكولات لإنتاج وإجراءات الفيبرين الغني بالصفائح الدموية، بالإضافة إلى معلومات حول تكلس الصفائح الدموية وتاريخ البلازما الغنية بالصفائح الدموية. الغرض من هذه الدراسة هو مناقشة إنشاء مركزات الصفائح الدموية هذه، وشرح نظرية عملها، وتقديم تحليل شامل حول هذا الموضوع في الأدبيات الحالية المتعلقة بالفم والوجه والفكين.

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INTRODUCTION

Cleft lip and/or palate (CL/P) is considered the most prevalent of the common human congenital craniofacial birth defects, Cleft lip, and cleft palate, and both together are included in the condition group known as an orofacial cleft. An opening in the upper lip that might reach the nose is present in a cleft lip. On the other hand, the cleft palate contains the roof of the mouth and an opening into the nose and occurs throughout a baby's development in the womb. The opening may be on one side, on both sides or in the middle. Researchers are unable to pinpoint the exact cause of cleft lip and palate. It can be brought on by environmental factors such as taking specific medications during pregnancy, smoking, or consuming alcohol during pregnancy as well as genes passed down from parents. Many surgeries and examinations are necessary for kids with cleft lip and palate. Clefts are often treated with surgery as well as extra therapies like speech therapy and dental care. A patient with cleft lip and palate may need several surgical procedures, depending on the nature and severity of the defect. In general, treatment comprises a combination of the procedures and the application of PRF, though scheduling and treatment will be tailored in line with each patient's unique medical needs. Many cytokines and growth factors that are released by platelet concentrates enhance the periosteum's ability for regeneration and speed up bone and tissue healing. Platelet-rich fibrin, which is produced by sequestering and concentrating is an autologous source of transforming growth factor beta and platelet-derived growth factor. [(1)]

Historical background of platelet concentrates

The use of blood-derived proteins to seal wounds and encourage healing began with the use of fibrin glues, which were initially reported more than 40 years ago and are made of concentrated fibrinogen (polymerization driven by thrombin and calcium**)** [(2)] As a result, Whitman *et al.* [(3)] pioneered the use of platelet concentrates to promote healing and replace fibrin glues. The first true platelet concentrate was Platelet-rich plasma (PRP) and was presented in the late 1990s [(4)]. Over 95% of PRP is made up of platelets, a type of cell that actively secretes growth factors to start the healing process of wounds as well as factors that promote cell adhesion, proliferation, and migration of different types of cells. [(4)] Platelets are rich in growth factors such as PDGF-AB (platelet-derived growth factor AB), TGFb-1 (transforming growth factor b-1), and VEGF (vascular endothelial growth factor), which can induce cell proliferation, matrix remodeling, and angiogenesis. In 2001, a new generation of platelet concentrates was introduced in France by Choukron et al. and was termed platelet-rich fibrin (PRF). It was initially employed exclusively in oral

and maxillofacial surgery. Because it was distinct from other concentrates, it was labeled a "second-generation" platelet concentrate and turned out to be a significant turning point in terminology development [5]. In 2006, Bielecki *et al.* and Cieslik-Bielecka *et al* described a Platelet Rich Gel (PRG) which was suggested to be a more physiologically activated fibrin matrix rich in platelets, leukocytes, and somewhat active chemicals. [6] In 2006 also, Sacco developed the Concentrated Growth Factor (CGF). In this technology, cells are separated using a pre-programmed centrifugation cycle in the range of 2400-2700. The obtained fibroblast blocks were significantly bigger, richer, and denser. [7]

Currently**, s**urgical operations in the medical and dental disciplines regularly involve the use of platelet concentrates (PC), especially in sports medicine, plastic surgery, and oral and maxillofacial surgery [8].2700. The obtained fibroblast blocks were significantly bigger, richer, and denser [7]**.**

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The evolution of platelet concentrates as mentioned in the literature

The evolution of platelet concentrates as mentioned in the literature can be summarized in detail in (Table 1).

Table (1): Evolution of platelet concentrates over the years

Year	Reference No.	Detailed information
1997	(9)	Whitman et al. initially called their item PRP while it was being prepared, but later changed the term when it attained the consistency of a fibrin gel as “platelet gel” [9].
1998	(10)	Up to the study by Marx and others, kicked off the demand for these strategies, the development of these techniques progressed slowly. However, without considering their architecture or content, all of these products were labeled as PRP, and this lack of nomenclature persisted for a long time. Some commercial businesses began identifying their products with distinctive commercial names to increase visibility [10].
1999	(11)	DM Dohan Ehrenfest; One of the well-publicized techniques for producing pure platelet-rich plasma was marketed as PRGF (plasma rich in growth factors) or preparation high in growth factors (Endoret, Victoria, Biotechnology Institute BTI, Spain). However, there were serious problems with this method due to the absence of precise pipetting procedures and poor ergonomics. Vivo stat PRF, another P-PRP technology that has drawn a lot of interest, is a commercial product (Alleroed, Denmark). However, contrary to what the name suggests, it creates PRP products rather than PRFs [11].
2000 2001	(5)	Based on the strong fibrin gel polymerization shown in this preparation, In France, Choukroun et al. created a different type of PC under the name PRF. PRF the initially employed in 2001 exclusively in oral and maxillofacial surgery. Because it was distinct from other PRPs, it was labeled as a "second-generation" platelet concentrate. This turned out to be a significant turning point in terminology development [5].
2002	(12)	According to Tang YQt 2002, it has "always been a widespread belief that the inclusion of leukocytes, or immune cells, in L- PRP or L-PRF would provide an added benefit compared to P-PRP or P-PRF. Does this imply that platelets have no function in immunity? The antimicrobial peptides Thymosin B4, Fibrino-peptides A and B, Connective tissue, Platelet Factor 4 Activation Chemokine (C-C motif) Ligand 5 and Peptide III are abundant in human platelets, according to numerous research [12].

2006	(6) (7)	PRP was classified as an inert substance.Whereas PRG (Platelet Rich Gel) was a more physiologically activated fibrin matrix that was rich in platelets, leukocytes, and somewhat active chemicals as described by Bielecki et al. and Cieslik-Bielecka et al.. [(6)]. Sacco developed a fresh CGF idea (Condensed growth factors). Cells were separated using rpm in the range of 2400-2700 for the venous blood generation of CGF. The obtained fibroblast blocks were significantly bigger, richer, and denser [(7)].
2008	(13)	Everts et al. concentrated on the platelet concentrate's leukocyte component and its two forms, not activated and activated. Platelet-leukocyte rich plasma (P-LRP), the name of the non-activated product, and platelet-leukocyte gel, the name of the activated gel, were both used (PLG) [(13)]
2009	(11)	Dohan Ehrenfest et al. put up the initial classification of platelet concentrate. This classification divided the products into 4 major categories based on the presence or absence of biological components (mainly leukocytes) and fibrin architecture. Pure PRF (P-PRF), leukocyte-poor PRF, leukocyte-and-platelet-rich plasma (L-PRP), pure platelet-rich plasma (P-PRP), or leukocyte-poor platelet-rich plasma (LP-PRP), leukocyte-and platelet-rich fibrin, and pure PRF (P-PRF) (L-PRF) [(11)].
2010	(14)	Sohn introduced the concept of sticky bone (autologous fibrin glue mixed with a bone graft) [(14)].
2012	(15) (16) (17)	Another classification, confined only relevant to PRP and used in sports medicine, was developed by Mishra et al. Based on the presence or absence of leukocytes and whether the PRP is activated, they identified 4 forms of PRP, all of which may be divided into two subtypes: A: Baseline if you have more than five platelets or type B: Baseline platelets 5. In each of the varieties that follow, "solution" refers to PRP not yet active and "gel" to turn on PRP. The four varieties are L-PRP solution, L-PRP gel, P-PRP solution, and P-PRP gel [(15)]. DeLong et al. unveiled the PAW classification scheme about the same time (Quantity of platelets, activation state, and presence of white cells). Although, it was limited to PRP families exclusively and followed a categorization method similar to that of Mishra et al [(16)]. At the last step of the coagulation cascade, fibrinogen molecules self-assemble into a highly biocompatible three-dimensional fiber network, which is exploited by fibrin gel. [(17)].
2014	(18) (19) (20) (21) (22)	Choukroun unveiled an improved PRF known as (A-PRF, which is said to include more monocytes.) [(18)]. T-PRF is a brand-new item that Tunal et al (Titanium prepared).Many materials have been used as tissue engineering scaffolds; hyaluronic acid, hydroxyapatite, PRP, and PRF. The The PRF clot's components, including fibrin, platelets, leucocytes, growth factors, and cytokines, are generally considered to have beneficial effects [(19)]. Among the growth factors present in the platelet-rich fibrin clot, PDGF, IGF, and TGF-b play the most significant roles. Periodontal soft and hard tissues that are undergoing regeneration express PDGF- and PDGF-R receptors. [(19, 20)]. Lower centrifugation rates were suggested by Ghanaati et al. in 2014 as a way to better concentrate growth factors and cells in the higher platelet-rich layers. To speed up the healing of surgical wounds, the ideas revolve around concentrating platelets and growth factors in a plasma solution and activating them in a fibrin gel· [(21)]. A second-generation platelet concentration known as PRF is frequently utilized to quicken wound healing. [(22)].
2015	(23) (24)	A thorough technical note on the preparation of injectable PRF was provided by Mouro et al. Rayan. Centrifuges that are more affordable and widely available in 2015 can generate clots, but they must also adhere compared to the first protocol. For this reason, such clumps ought to be referred to as PRF like products, a name that might be incorporated into the most recent worldwide categorization (PDF) Temperature and Dimensions of Platelet Rich Fibrin (PRF) Clots Generated due to Three Centrifuges [(23, 24)].
2016	(25) (26) (27)	In a recent study, Yajamanya et al. used a cellblock cytology technique to compare the fibrin variations in PRF network patterns in young and old age groups. They demonstrated that as people aged, fibrin networks became noticeably less thick and more flexible. Additionally, they found that as age groups increased, less platelets and WBCs were trapped within fibrin networks. While the pilot and study proper sections were both included in Rayan Hamid's thesis study [(24)]. The pilot research was done to establish standards. A total of five human volunteers and sheep were used in the investigation [(25-24)]. Amol M. Doiphode. Comparatively to PRP, the preparation of PRF is less time-consuming, less expensive, and produces good results. Both PRP and PRF can be used in conjunction with extraction sites for the third molars of the human mandible to improve wound healing and osseous regeneration [(26)]. H. Shawky and SA Seifeldin Autogenous bone and PRF worked well together to improve bone density is not increased by the amount of newly produced bone in alveolar cleft restoration· [(27)]
2017	(28)	The primary biological distinction between PRP and PRF is that although the polymerization in PRP is intentionally induced and involves the enmeshment of extrinsic growth factors, the

		polymerization in PRF occurs naturally and involves the enmeshment of intrinsic growth factors. Compared to in-vitro [28].
2018	(29)	According to Maryam Omidkhoda, the use of PRF had no appreciable impact on the maxillary alveolar graft's thickness, height, or density. Moreover, Maryam stated that three months following surgery, the use of PRF gel in conjunction with the autogenous bone graft in the cleft site had no appreciably different impact on the quantity and quality of the graft there [29].
2019	(30)	Mohammed Soliman. According to studies on how primary cleft palate repair wound healing is affected by platelet-rich fibrin (PRF), the use of platelet-rich fibrin (PRF) in conjunction utilizing an autologous bone graft appears to be a successful, secure, and affordable method for recurring cleft palate fistulas being closed [30].
2020	(31)	Richard J.Miron, Cell layer separation was found to be considerably impacted by patient variation in baseline platelet, leukocyte, and erythrocyte counts (hematocrit). This result became more apparent at slower centrifugation speeds [31].
2021	(32)	Alaa Z. Makki, PRF significantly reduced postoperative pain and the need for analgesics and enhanced soft tissue healing at extraction sockets [32].
2022	(33)	Esraa Zalama, PRF improved marrow cavity reconstruction, remodeling, defect bridging by bicortical callus, and defect reduction while probably assisting in the production of a massive low-density callus. Additionally, the PRF's action is amplified by the addition of ZnONPs, which hasten bone growth and improve bone quality and density [33].

Current classification of platelets concentrates:

Dohan Ehrenfest *et al.* put the first classification for platelet concentrates [11]. Depending on their cell content and architecture, the main groups of preparations can be identified following the classification as Dohan *et al.* [11, 34] proposed:

1. Leukocyte-poor PRP, also known as pure PRP (P-PRP), is a preparation without leukocytes.

2. Leukocyte-based preparations include PRP and leukocytes. The majority of experimental or commercial systems belong to this family.

3. Pure PRF or leukocyte-deficient PRF

4. Preparations called L-PRFs are PRFs with leukocytes and a high-density fibrin network.

Platelet-rich fibrin (PRF) preparation protocol:

The protocol for the preparation of PRF is a straightforward technique free of anticoagulants produced by Choukroun *et al.* in France [35]. In the absence of anticoagulants, fibrin polymerization and platelet activation begin right away. Hence, following centrifugation three layers are created; a basal layer of RBCs, a top layer of acellular plasma, and an intermediate PRF clot (Figure 1).

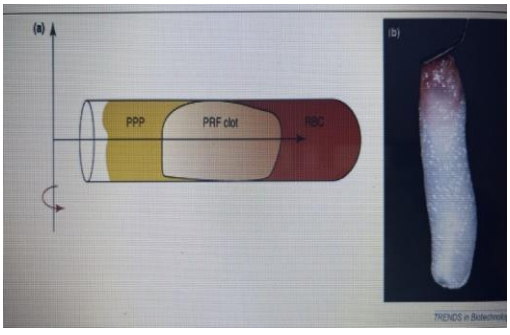

Figure (1): Platelet-rich fibrin (PRF)

The PRF clot produces a dense fibrin matrix that contains the bulk of the platelets

and leucocytes from the retrieved blood. which has a complex three-dimensional design. **(36, 19)** The PRF clot transforms into a robust membrane when sandwiched between two gauzes. It can be used in oral and maxillofacial (37, 38) and cosmetic surgery (39).

The goal of the procedure is to form a fibrin clot out of released cytokines and platelets. **(40)**. Only centrifuged blood with no additional anticoagulant or bovine thrombin is required by the PRF technique. **(41)** Then, a blood sample without anticoagulant is collected in 10-mL tubes and placed in glass or plastic with a glass coating (41, 36, and 42). Following this, the tubes are immediately centrifuged for 10 minutes at 3,000 rpm (43, 41). The ability of platelet-rich fibrin to form an autogenous membrane sets it apart from other fibrins. This membrane serves as a physical barrier and permits clean contact with the mouth. It can also encourage the repair of bone and soft tissue. Its usage in individuals with cleft lip and palate as a stimulant and barrier for the alveolar bone graft's growth is a promising method.

The use of platelet-rich fibrin in cleft lip and palate patients:

Cleft lip and/or palate is a common congenital condition with a complicated origin. The management of this disease is difficult due to a variety of circumstances. The primary goal of treatment is largely functional in the sense of establishing a normal feeding pattern, becoming acquainted with normal hearing, and so developing normal speaking. These objectives have a significant impact on the patient's and his family's social and psychological well-being. Many materials, including hyaluronic acid, hydroxyapatite, PRP, and PRF, have been employed as tissue engineering scaffolds. They promote bone repair by activating undifferentiated mesenchymal cells (44). Cleft demands a long-term treatment plan and multidisciplinary management by a qualified cleft team. Specialists from the major areas of cleft care should collaborate to give the child a pleasant outcome and self-confidence that comes out from intelligible speech, healthy teeth, and pleasant facial appearance (45). Clark *et al.* (46) conducted a retrospective evaluation of patients who had large cleft palates repaired using decellularized dermal allograft. It has been shown to be both safe and effective in the primary closure of broad clefts affecting both the hard and soft palates. Its application in the repair of an existing fistula is promising. PRF has lately been employed in maxillofacial and plastic surgery to benefit from the continual release of growth factors that improve wound healing over time without causing inflammatory reactions. In vitro, it was mixed with bone grafts and demonstrated excellent potential for cell adhesion, proliferation, and differentiation of osteoblasts. Glicerio *et al.* (47) conducted an experimental, prospective, longitudinal study on 11 recurrent cleft palate fistulas

from April 2008 to July 2010 on 11 recurrent cleft palate fistulas using local mucoperiosteal flap with the addition of PRGF gel mixed with autologous bone graft and placed between two sheets of solid collagen filling the bone defect between the palatal and nasal mucosa complete closure of palate fistulas were achieved. The use of PRGF combined with autologous bone graft appears to be an effective, safe, and low-cost treatment for recurrent cleft palate fistula closure. PRF is made of an autologous bioscaffold of a dense fibrin matrix with integrated growth factors, which are released from the scaffold over a sustained period to progress the healing of hard and soft tissues (Clark *et al.* [46]; Canellas et al., [48]). A modification of the centrifugation protocol was proposed in 2017 (Ghanaati *et al.* [49]), The novel formulation of advanced PRF (a-PRF) was developed, releasing in vitro noticeably more growth factors than traditional PRF (Kobayashi *et al.*) [34]. The a-PRF membrane's increased neutrophilic granulocyte cell distribution may be the reason for the improved functionality of the transplanted monocytes/macrophages and lymphocytes and their deployment to facilitate tissue regeneration (Ghanaati *et al.*) [49]. Additionally, according to Kobayashi *et al.* [34] and El Bagdadi et al. [50], the increased growth factor releases of the PRF membrane could have a good impact on tissue regeneration using biomaterials. A standardization of PRF protocols is needed to carry out studies that can be replicated and have a higher level of scientific evidence (Ghanaati et al. [49]). The use of platelet-rich fibrin (PRF) as a scaffold for human osteoblast carriers has also been investigated. PRF membranes were used to support human osteoblasts' metabolic activity and proliferation to a notable degree [50]. Recently, it was shown that PRF controls the expression of the proteins HSP47 and LOX in human osteoblasts. These proteins promote cell proliferation, matrix formation, and adhesion. Thus, PRF may support bone regeneration, repair, and healing [51].

CONCLUSION

In conclusion platelet-rich fibrin appears to be a well-liked minimally invasive procedure with low risks and acceptable clinical outcomes. From a therapeutic perspective, this biomaterial seems to hasten physiologic repair, and many potential applications of PRF can be used in several clinical scenarios.

Declaration of interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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