Journal of Hygienic Engineering and Design

Original scientific paper
UDC 616.314-089.843:547.962.9

SECOND GENERATION PLATELET CONCENTRATE (PLATELET-RICH FIBRIN) IN ITS APPLICATION IN ORAL SURGERY

Biljana Evrosimovska[1*], Daniela Veleska-Stevkovska[2], Cena Dimova[3], Zaklina Menceva[1]

[1]Department of Oral surgery and Implantology, University Dental Clinical Centre St. Pantelejmon, Mother Tereza 17, 1000 Skopje, Macedonia
[2]Faculty of Dentistry, University Ss. Cyril and Methodius, Mother Tereza 17, 1000 Skopje, Macedonia
[3]Faculty of Medical Sciences, Dental medicine, University Goce Delcev, Krste Misirkov 10-a, 2000 Stip, Macedonia

[*]e-mail: bevrosimovska@gmail.com

Abstract

The development of bioactive surgical additives, which are being used to regulate the inflammation and increase the speed of healing process, is one of the great challenges in oral surgery. Platelet-rich fibrin (PRF) is a second-generation platelet concentrate who was defined as an autologous leukocyte and PRF biomaterial, in which, platelets and leukocytes are collected with high efficiency such that the growth factors will able to release gradually during at least 1 week. The biologic effect of this fibrin matrix is: angiogenesis, immune control, harnessing the circulating stem cells, and wound protection by epithelial cover. The following article attempts to summarize our clinical cases regarding the technique of using PRF, focusing on its preparation, advantages of using it in oral surgery.

Three cases with different clinical diagnoses were taken for this study in order to show the possible ways of application of PRF in the surgical field. In the first case, it is a 53 year-old female patient who has been diagnosed with osteonecrosis of the alveolar ridge during the examination in the projection of the first lower right molar. In the second case, PRF application was administered to a 41 year-old female patient diagnosed with radicular cyst on the upper left second incisor. The third case involved a 47 year-old male patient with diagnosed gangrenous roots in the upper right first and second premolars ant the second molar in which the PRF application was intended to achieve alveolar bridge augmentation. PRF was prepared with blood drawn from individuals using technique du to PRF protocol. Both types of PRF (I and A-PRF) were applied independently in the first case, and in the second and third cases a bone graft was placed together with PRF.

The soft and bone tissue management in all our cases show process of neovascularization through the PRF clot and the epithelial covering development. In spite of the infectious and inflammatory statement of such sockets, rapid healing of the wound was observed without pain, dryness, or purulent complications. The results of the observed cases showed that biologic effect of PRF was revealed trough achieved angiogenesis, immune control, harnessing the circulating stem cells, and wound protection by epithelial cover.

PRF alone or in combination with other biomaterials seems to have several advantages and indications in oral surgery, due it is a minimally invasive technique with low risks and satisfactory results.

***Key words**: Platelet-rich fibrin, Blood platelet, Bone regeneration, Soft tissue regeneration.*

1. Introduction

Various biomaterials have been used for bone and tissue regeneration in addition to autogenous and allogenic grafts but not a single graft material is considered as gold standard for the treatment of intrabony and soft tissue defects.

Platelet-rich fibrin (PRF) which belongs to a second generation of platelet concentrates [1, 2], was first

developed in France, by Dr. Choukroun *et al.*, in 2000 [3], for specific use in oral and maxillofacial surgery. PRF is a new generation of platelet concentrate techniques that allow one to obtain fibrin membranes enriched with platelets and grow factors, starting from an anticoagulant-free blood harvest [4].

PRF has a dense fibrin network with: leukocytes, cytokines, structural glycoproteins [5], and also growth factors such as transforming growth factor β1, platelet-derived growth factor, vascular endothelial growth factor and glycoproteins such as thrombospondin-1 [6]. Leukocytes that are concentrated in PRF scaffold play an important role in growth factor release, immune regulation [7], anti-infectious activities [8], and matrix remodeling during wound healing.

The PRF clot forms a strong natural fibrin matrix, which concentrates almost all the platelets and growth factors of the blood harvest [7, 9] and shows a complex architecture as a healing matrix with unique mechanical properties which makes it distinct from other platelet concentrates.

PRF has immune functions like chemotaxis as leukocytes present in PRF degranulates during activation and releases cytokines like IL-1, IL-4, IL-6 and TNF-α. PRF also contains anti-inflammatory cytokine such as IL-4 which requires further research [7]. PRF has been described as "an immune and platelet concentrate in a single fibrin membrane, containing all constituents of the blood sample favorable for healing and immunity" [10].

The leukocytes present within PRF play a role as an anti-infective action, immunological regulation, ability to produce a great number of vascular endothelial growth factors (VEGF), which has caught the interest and curiosity of researchers [11, 12].

Another added advantage of PRF is the presence of natural fibrin network in PRF which protects the growth factors from proteolysis [13, 14]. PRF also favors the development of micro vascularization leading to a more efficient cell migration.

PRF dissolves slowly after use, keeping it stable for a longer period of time, preserving the fibrin mesh, allowing longer cytokine life and a higher concentration of platelets, leukocytes, circulating stem cells incorporated within the physiological matrix of fibrin. Consequently, growth factors are allowed to be released more slowly at the surgical site, persisting for a longer time during wound cicatrisation, from 7 to 28 days [15, 16].

The following article attempts to summarize the relevant literature regarding the technique of using platelet rich fibrin (PRF), focusing on its preparation, and advantages of using it in clinical applications in oral surgery.

2. Materials and Methods

The study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from the patient after a thorough explanation of the nature, risks, and benefits of the clinical application.

2.1 Materials (patients)

Three cases with different clinical diagnoses were taken for this study in order to show the possible ways of application of PRF in the surgical field. In the first case, it is a 53 year-old female patient who has been diagnosed with osteonecrosis of the alveolar ridge during the examination in the projection of the first lower right molar. In the second case, PRF application was administered to a 41 year-old female patient diagnosed with radicular cyst on the upper left second incisor. The third case involved a 47 year-old male patient with diagnosed gangrenous roots in the upper right first and second premolars ant the second molar in which the PRF application was intended to achieve alveolar bridge augmentation.

2.2 Methods

2.1.1 PRF protocol

The PRF protocol is very simple. A blood sample was taken without anticoagulant in 10 mL tubes, which were immediately centrifuged at different rotation per minute according to what kind of PRF was made (Figure 1). A-PRF tubes (red tubes) used to get clots and make membranes and I-PRF tubes (orange tubes) used to get liquid PRF for injection. The tubes were under vacuum and the blood stops being collected when the tubes were full. The blood drawing has to be as fast as possible. It's essential for the PRF clot quality.

Figure 1. PRF centrifuge by Dr. J. Choukroun with A-PRF tubes (red tubes) and I-PRF tubes (orange tubes)

PRF production protocol attempts to accumulate platelets and the released cytokines in a fibrin clot [17]. They mostly accumulate in the lower part of the fibrin clot at the junction between the red corpuscles (red thrombus) and the PRF clot itself. It turns out that the PRF red extremity would be even more effective than the higher part of the fibrin clot.

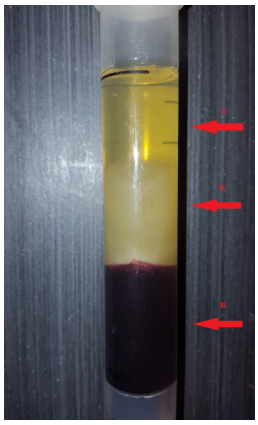

Figure 2. Layers of centrifuged blood samples, tube with three fractions: a) supernatant-acellular plasma at the top, b) fibrin clot in the middle of the tube, c) red corpuscles at the bottom

The duration of time between blood collection and centrifugation process was an important parameter affecting the success and clinical outcome of this procedure. The absence of anticoagulant implied the activation in a few minutes of most platelets of the blood sample in contact with the tube walls and the released of the coagulation cascades. Slow handling of blood to centrifugation process is resulting in diffuse polymerization of fibrin leading to the formation of a small blood clot with irregular consistency.

Working temperature must be between 21 and 30 ^{0}C, because the clot cannot be produced if the temperature is lower.

Number of collected tubes was minimum at least 2, and maximum 12, always set balanced 2 by 2 because in contrary, there will be vibrations during the centrifugation. We used the color code to balance the tubes easily.

2.1.2 Protocol for A-PRF

The centrifuge must be set at 13 x 100 rpm/8 minutes. At the end of centrifugation, the lid was opened automatically. After that we removed the tube and the caps, and placed the tubes in the sterile tube holder and let it them to "rest" around 5 minutes.

- PRF clots removal:

First, we took the fibrin clot into the opened tube with the sterile PRF forceps and separated the fibrin clot from the red cells. We placed the clot on the mini-tray covered with a gauze and use the closed scissors to peel off the red clot (Figure 3). The PRF clots were putted on the BoX grid, covered with the tray and then we putted the lid on.

The PRF BoX was used to:

- Get membranes of constant thickness and kept them always hydrated and to remain them intact for 2 or 3 hours (not to be dehydrated).

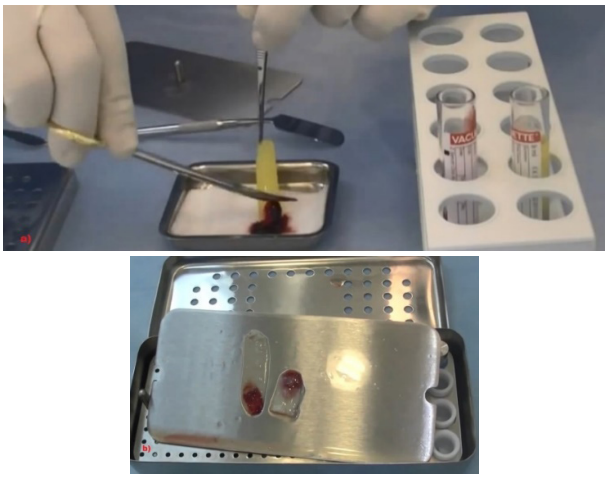

Figure 3. a) Removing red part from PRF clot, b) PRF membrane

- Recover the exudate and
- Produce "plugs" of PRF for socket extraction filling (which was done in the white cylinders, with the piston).

We kept the exudate recovered at the bottom of the box in order to:

- Hydrate biomaterials,
- Flush the surgical sites, sockets and cysts and
- Preserve the autogenous bone blocks (rather than in saline).

2.1.3 Protocol for I-PRF

The centrifuge must be set at 7 x 100 rpm/3 minutes. At the end of the spin, supernatant was formed on the surface of the orange tube. In order to collect the liquid, we penetrated the cap with a 21G needle (green) mounted on a syringe. Needle was placed in the middle of the I-PRF supernatant, against the wall of the tube for better visibility. Aspiration was done until the level of the red blood cells raises up to the needle bevel. I-PRF remained liquid for about 10 -12 minutes, then clotted. The injection was done before the end of these 10 - 12 minutes (Figure 4).

Figure 4. Aspiration of I-PRF

We used the I-PRF for injection: a). into the soft tissues b). in the bone graft where we mix the granules with the A-PRF, and poured the I-PRF drop by drop for avoiding an overflow. After that we waited a few seconds and continued until we obtained the complete coagulation of the biomaterials (in less than a minute) c). into the sinus, after the filling. The granules were fixed and coagulated, and d). I-PRF was used to coagulate the biomaterials before application.

3. Results and Discussion

3.1 Results - clinical cases

In surgical procedures, PRF could serve as a resorbable membrane for guided bone regeneration (GBR), preventing the migration of non-desirable cells into bone defect and providing a space that allows the immigration of osteogenic and angiogenic cells and permits the underlying blood clot to mineralize.

Figure 5 shows the case of wound with osteonecrosis after tooth extraction done in patient with diabetes mellitus. The epithelization of the wound was not successfully attained even after 3 mounts of the extraction and necrotic bone was formed. A surgical procedure was performed with abolishing of the necrotic bone till getting to the healthy tissue and making bloody area on which PRF membrane was applied. Quickly, a neovascularization formed through the PRF membrane and the epithelial covering developed. Finally, in spite of the infectious and inflammatory statement of such defect, rapid healing of the wound was observed without pain, dryness, or purulent complications.

A current clinical example deals with the filling of bone defect with PRF caused by radicular cyst (Figure 6). After removal of inflammation tissue, the bone defect was grafted with sticky bone, mass of grafting material combined of Bio-OSS and PRF exudate. The PRF exudate was collected in the bottom of PRF box during straining of PRF membranes. It is very rich in proteins (fibronectin and vitronectin). PRF exudate was than applied drop by drop on the bone substituent and left to indurate together. That kind of mass was insert in bone cavity and covered with PRF membrane. All that was covered with mucoperiosteal flap and sutured. Control examine reveal fine healing wound, without any symptoms of inflammation.

In the figure 7 is shown case of preservation of the extraction sockets and augmentation of alveolar ridge in the maxilla in region of tooth's 14, 15 and 17. After extraction of the teeth, mucoperiosteal flap was done. Extraction sockets were fulfilled with sticky bone, which was covered with Bio-Oss collagen membrane and above all that PRF membrane was lay on. The flap was repositioned to its presurgical level and sutured with atraumatic silk string. Clinical healing was normal with neither inflammation nor untoward clinical symptoms. Postoperative clinical parameters showed that application of PRF achieved formation of new bone tissue and enough keratinized gingiva. It was therefore natural to capture whole volume of monocytes in the PRF, to make it more active in stimulating bone grafts, but also to turn to a more rapid transformation of monocytes into macrophages to increase the effect bone stimulation.

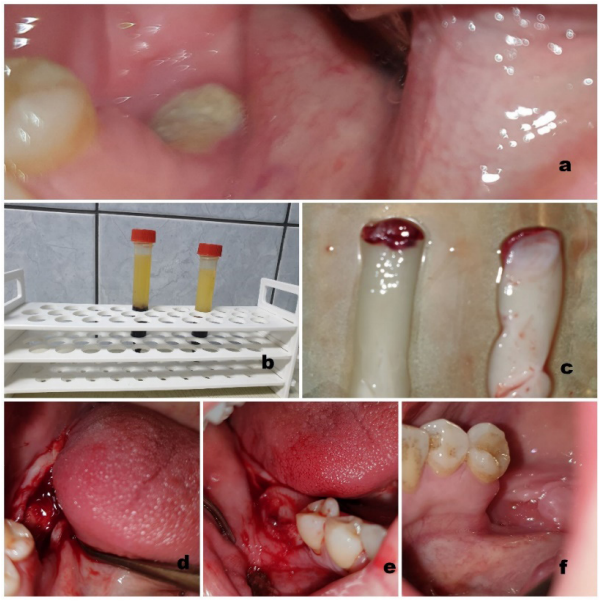

Figure 5. a) Bone surface with osteonecrosis, b) PRF tubes, c) PRF membranes, d) Removed bone with osteonecrosis, e) Applied PRF membrane, f) Status postoperative after one mount with formation of new soft tissue

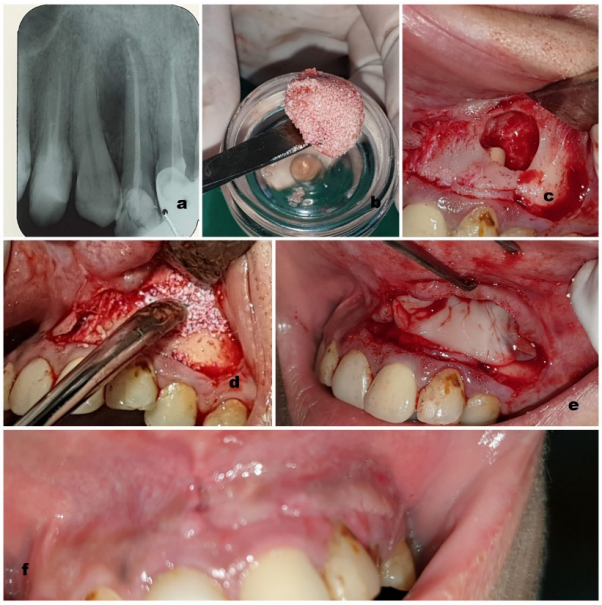

Figure 6. a) Retro alveolar X-Ray of tooth 22, b) Sticky bone, c) Bone defect after enucleation of the radicular cyst and resection of the tooth apex, d) Done cavity filled with sticky bone, e) Sticky bone covered with PRF membrane, f) Post-operative status after two weeks

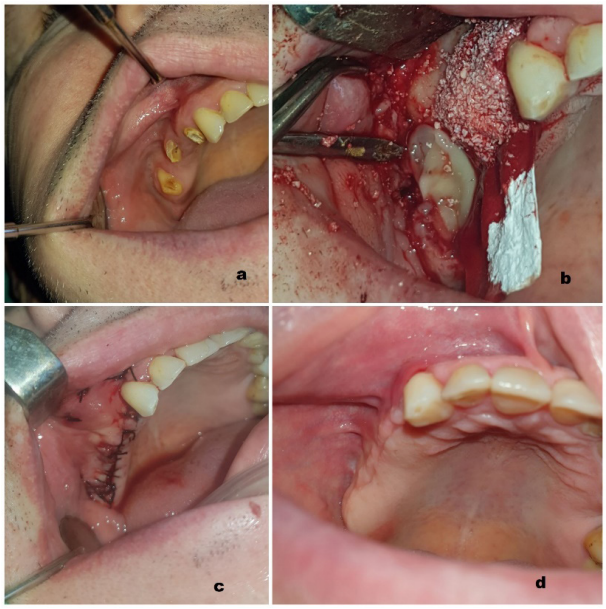

Figure 7. Preservation of the extraction wound and augmentation of alveolar ridge: a) Status intraorally, radix gangrenosa 14, 15, 17, b) Applied sticky bone covered with Bio-Oss Collagen membrane and PRF membrane, c) Set suture, d) Post-operative status after 3 weeks

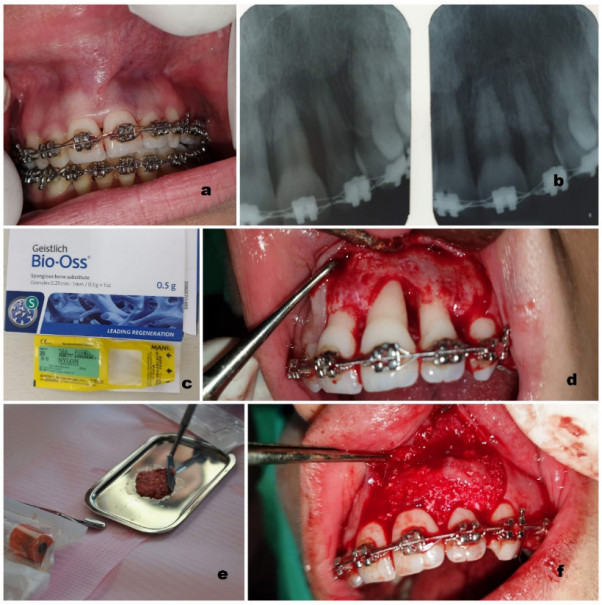

Figure 8. a) Bony defect due to fix orthodontic bracelets, b) X-Ray before and after surgical intervention, c) Bone grafted material and suture used in intervention, d) Absence of the bone around the roots of first and second maxillary incisors, e) Made sticky bone, f) Applied sticky bone in the defect

In figure 8 was presented a case where bony defect was consequence of wearing fix orthodontic bracelets. X-ray revealed lack of bone around the roots of first and second maxillary incisors. Incision was made corresponding to the number of adjacent one defect, extending to the line angles of both adjacent teeth that had no defect. Sticky bone made of spongious bone substitute and PRF exudate was applied in the bony defect and above that PRF membrane was lie on. Then, the mucogingival flap was repositioned as coronally as possible without tension with 6-0 nylon sutures. Patient was advised to abstain from brushing and flossing around the surgical area until suture removal (14 days after surgery). Control X-ray after 2 mounts showed formation of new bone tissue.

3.2 Discussion

The use of platelet concentrates for healing, improvement and regeneration of the soft and hard tissues in oral cavity is one of the latest achievements in dentistry [18].

In our study we used PRF plugs in the sockets of extracted maxillary roots and oral cavity after removal of periapical lesion of tooth 22. With the use of PRF as a socket preservation material in our cases we confirmed that PRF enhances healing of soft and hard tissue and reduced postoperative complications. Our results are in correspondence with Sharma *at all.*, and Moraschini and Barboza, [19, 20].

A-PRF+ and I-PRF are widely used either as a prophylactic measure in terms of socket preservation [21] after tooth extraction to prevent jaw atrophy and support the wound healing or in combination with bone substitute materials [22] to accelerate and enhance the regeneration process in the bone augmentation bed and to provide enhanced bone formation. Moreover, soft-tissue regeneration in periodontology is a further representative field for the application of PRF-based matrices. In this context, PRF-based matrices are disseminated in the treatment of chronic periodontitis [23] and the regeneration of gingival recession [24].

Furthermore, necrosis, such as bisphosphonate-associated osteonecrosis of the jaw, suffers from limited vascularization and impaired wound healing [28]. However, with the introduction of PRF, further minimal invasive possibilities became available for clinical application. Consequently, the use of PRF as a membrane or I-PRF injections showed promising clinical outcomes [29].

Thus, the application of A-PRF+ and I-PRF as a "biocatalyst" within the impaired region could accelerate the wound healing by providing the needed cells immediately after injury so that less cell recruitment is required. The combination with biomaterials is a promising approach in guided bone and tissue regeneration to enhance the capacity of the applied biomaterials and to enhance their bioactivity [22].

When we used PRF membranes in our cases for performing ridge augmentation, we used them to protect and stabilize the graft materials. The membranes act as fibrin bandages, accelerating the healing of the soft tissues, facilitating the rapid closure of the incision despite a substantial volume of added bone.

The use of PRF during surgery increases their numbers attentional stage so healing there by playing a central role in the phagocytosis of debris, microbes and necrotic tissues, as well as directing the future regeneration of these tissues through release of cytokines and growth factors.

Recently, studies have demonstrated that the PRF membrane has a very significant slow sustained release of many key growth factors (GF) for at least 1 week [6] and up to 28 days, [23] which means that PRF could release GF with its own biological scaffold for wound healing process.

PRF membrane helps in wound healing, protecting the surgical site [24], and promoting soft tissue repair; when mixed with bone graft, it may act as a "biological connector", which attracts stem cell, favors the migration of osteoprogenitor cells to the center of the graft, and provides a neo-angiogenesis [25].

Cut PRF membranes in fragments and mixed with the graft material, who were applied in the surgical side in the second and third case were function as a biological connector between the different elements of the graft, and as a matrix which favors neo-angiogenesis, the capture of stem cell, and the migration of osteo-progenitor cells to the center of the graft. These findings are in correlation with the results of Vence *at all.*, and Hamdan *at all.*, [26, 27].

Using the reported protocol, we observed high degree of gingival maturation after healing with a thickening of keratinized gingival tissue that improved the esthetic integration and final result of their prosthetic rehabilitation.

4. Conclusions

- Our clinical cases showed that PRF can be routinely used in oral surgery, with good biological effect and satisfactory clinical results under correct manipulation. PRF after extraction improves the bone width and height and bone quality.

- We concluded that PRF alone or in combination with other biomaterials seems to have several advantages and indications in oral surgery, due it is a minimally invasive technique with low risks and satisfactory results.

5. References

[1] Marx R. E., Carlson E. R., Eichstaedt R. M., Schimmele S. R., Strauss J. E., Georgeff K. R. (1998). *Platelet-rich plasma: Growth factor enhancement for bone grafts*. Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 85, pp. 638-646.

[2] Soffer E., Ouhayoun J. P., Anagnostou F. (2003). *Fibrin sealants and platelet preparations in bone and periodontal healing*. Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 95, pp. 521-528.

[3] Choukroun J., Adda F., Schoeffler C., Vervelle A. (2000). *An opportunity in paro-implantology: PRF* (in French). Implantodontie, 42, pp. 55-62.

[4] Su N. Y., Yang L. C., Chang Y. C. (2017). *Platelet-rich fibrin is the first-line treatment option for periodontal regeneration*. Journal of Dental Sciences, 12, pp. 203-204.

[5] Dohan E. D. M., Diss A., Odin G., Doglioli P., Hippolyte M. P., Charrier J. B. (2009). *In vitro effects of Choukroun's PRF (platelet-rich fibrin) on human gingival fibroblasts, dermal prekeratinocytes, preadipocytes, and maxillofacial osteoblasts in primary cultures*. Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 108, pp. 341-352.

[6] Dohan E. D. M., de Peppo G. M., Doglioli P., Sammartino G. (2009). *Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): A gold standard to achieve for all surgical platelet concentrates technologies*. Growth Factors, 27, pp. 63-69.

[7] Dohan D. M., Choukroun J., Diss A., Dohan L. S., Dohan J. J. A., Mouhyi J., Gogly B. (2006). *Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part III: eucocyte activation: A new feature for platelet concentrates?* Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 101, pp. 51-55.

[8] Moojen D. J., Everts P. A., Schure R. M.., Overdevest P. E., van Zundert A., Knape A. T. J., Castelein M. R., Creemers B. L., Dhert A. J. W. (2008). *Antimicrobial activity of platelet-leukocyte gel against Staphylococcus aureus*. J. Orthop. Res., 26, pp. 404-410.

[9] Dohan D. M., Choukroun J., Diss A., Dohan L. S., Dohan J. J. A., Mouhyi J., Gogly B. (2006) *Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: Platelet related biologic features*. Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 101, pp. 45-50.

[10] Werther K., Christensen I. J., Nielson H. J. (2002). *Determination of vascular endothelial growth factor (VEGF) in circulating blood: Significance of VEGF in various leucocytes and platelets*. Scand. J. Clin. Lab. Invest., 62, pp. 343-350.

[11] Kuhl S., Walter C., Acham S., Pfeffer R., Lambrecht T. J. (2012). *Bisphosphonate related osteonecrosis of the jaw-a review*. Oral Oncology, 48, pp. 938-947.

[12] Subramanian G., Cohen H. V., Quek S. Y. (2011). *A model for the pathogenesis of bisphosphonate-associated osteonecrosis of the jaw and teriparatide's potential role in its resolution*. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 112, pp. 744.

[13] Dohan E. D. M., Rasmusson L., Albrektsson T. (2009). *Classification of platelet concentrates: From pure platelet-rich plasma (PPRP) to leucocyte- and platelet-rich fibrin (L-PRF)*. Trends Biotechnol., 27, pp. 158-167.

[14] Lundquist R., Dziegiel M. H., Agren M. S. (2008). *Bioactivity and stability of endogenous fibrogenic factors in platelet-rich fibrin*. Wound Repair Regen., 16, pp. 356-363.

[15] Ling H., Ye L., Xiulian H., Yu Z., Hui W. (2009). *A comparative study of platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) on the effect of proliferation and differentiation of rat osteoblasts in vitro*. Oral Surg., Oral Med., Oral Pathol., Oral Radiol., and Endod., 108, pp. 707.

[16] Everts P. A. M., Zundert A., Schonberger J. P. A. M., Devilee R. J. J. (2008). *What do we use: Platelet-rich plasma or platelet leukocyte gel?* J. Biomed. Mater Res. A, 85, pp. 1135-1136.

[17] Giannobile W. V. (1996). *Periodontal tissue engineering by growth factors*. Bone, 19, (1 Suppl.), pp. 23-37.

[18] Kiran NK, Mukunda KS, Tilak RN. *Platelet Concentrates: A Promesing Inovation in Dentistry*. Journal of Dental Sciences and Research 2011; 2(1): 50-61.

[19] Sharma M, Lone PA, Singh R, Waheed A, Patil V. *Effect of autologous platelet rich fibrin in bone regeneration in post-extraction mandibular sockets*. International Journal of Applied Dental Sciences 2018; 4(3):309-313.

[20] Moraschini V and Barboza ESP. *Effect of autologous platelet concentrates for alveolar socket preservation: asystematic review*. Int J Oral Maxillofac Surg 2015; 44(5):632-41.

[21] Yelamali T., Saikrishna D. (2015). *Role of platelet rich fibrin and platelet rich plasma in wound healing of extracted third molar sockets: A comparative study*. J. Maxillofac. Oral Surg., 14, pp. 410-416.

[22] Zhang Y., Tangl S., Huber C. D., Lin Y., Qiu L., Rausch-Fan X. (2012). *Effects of Choukroun's platelet-rich fibrin on bone regeneration in combination with deproteinized bovine bone mineral in maxillary sinus augmentation: A histological and histomorphometric study*. J. CranioMaxillofacial Surg., 40, pp. 321-328.

[23] Sharma A., Pradeep A. R. (2011). Treatment of 3-wall intrabony defects in patients with chronic periodontitis with autologous platelet rich fibrin: A randomized controlled clinical trial. J. Periodontol., 82, (12), pp. 1705-1712.

[24] Eren G., Atilla G. (2013). *Platelet-rich fibrin in the treatment of localized gingival recessions: A split-mouth randomized clinical trial*. Clin. Oral Investig., 18, pp. 19411948.

[25] Toffler M., Toscano N., Holtzclaw D., Corso M. D., and Dohan E. D. M. (2009). *Introducing Choukroun's platelet rich fibrin (PRF) to the reconstructive surgery milieu*. J. Implant. Clin. Adv. Dent., 1, pp. 21-30.

[26] Vence BS, Mandelaris GA, Forbes DP. *Management of dentoalveolar ridge defects for implant site development: An interdisciplinary approach.* Compend Ed Dent 2009; 30(5):250-262.

[27] Hamdan AA-S, Loty S, Isaac J, Bouchard P, Berdal A, Sautier J-M. *Platelet-poor plasma stimulates proliferation but inhibits differentiation of rat osteoblastic cells in vitro.* Clin Oral Impl Res 2009; 20:616-623.

[28] Mucke T., Krestan C., Mitchell D., Kirschke J., Wutzl A. (2016). *Bisphosphonate and Medication-Related Osteonecrosis of the Jaw: A Review*. Semin. Musculoskelet. Radiol., 20, pp. 305-314.

[29] Soydan S. S., Uckan U. (2014). *Management of bisphosphonate-related osteonecrosis of the jaw with a platelet-rich fibrin membrane: Technical report*. J. Oral Maxillofac. Surg., 72, pp. 322-326.