Special Issue Impantology - Platelet rich Fibrin

With this issue, we want to introduce a new Panorama series. Three times a year, we will present in more detail particularly exciting current master's theses prepared at the IMC. The original abstract and the corresponding references will be made available unchanged. As a special highlight, the editorial team will also provide a comprehensive overview on the clinical background. In addition, corresponding clinical tips and tricks and, where appropriate, links to interesting manufacturers and products will be integrated.
We want to start this new series with a topic that comes up again and again - the use of platelet rich fibrin preparations - on the one hand for better healing after the removal of wisdom teeth, but also as an option for alveolar ridge preservation. After finishing the master's thesis, this work was expanded to perform a meta-analysis with a specific focus on different protocol options. The final analysis was published in 2023 in the renowned Journal of Oral and Maxillofacial Surgery (Al-Badran, A., Bierbaum, S., Wolf-Brandstetter, C. (2023). Does the choice of preparation protocol for platelet-rich fibrin have consequences for healing and alveolar ridge preservation after tooth extraction? A meta-analysis. Journal of Oral and Maxillofacial Surgery, Volume 81, Issue 5, May 2023, Pages 602-621.) For interested readers the authors can send the PDF version as private copy on request.
We hope you will enjoy reading and find some new details or interesting links.

Prof. Dr. Joos (Editor)

Scientific Background

In oral surgery, the surgical removal of mandibular third molars (MTM) is considered as one of the most common surgical interventions. In the early postoperative stage, patients usually suffer from considerable complications, including pain, edema, trismus and alveolar osteitis. Several attempts including preoperative and postoperative antibiotics, osteotomy, analgesics, using different flap techniques, laser and cryotherapy or postoperative ice packs have been used to reduce these complications.
Besides third molar extraction, extraction of other teeth is a commonly performed procedure required in case of root damage, severe periodontal defects among others. The removal of a tooth is known to induce alveolar ridge loss followed by changes in the overlying soft tissue (Schropp et al. 2003). Alveolar bone atrophy may have a considerable effect on tooth replacement therapy, especially when implant supported restorations are planned in the esthetic zone. To reduce such undesired consequences of tooth extraction and to improve success rates of planned implantations, alveolar ridge preservation (ARP) has been proposed. Two important factors influence the selection of ARP material after tooth extraction, cost-effectiveness of the graft and the influence on the final implantation outcomes.
Platelet-rich fibrin (PRF) was introduced as a strategy to improve the overall healing process in third molar extractions and for the purpose of ARP as well. It is an autologous material derived from patient´s own blood (Dohan et al. 2006) and was originally developed as a second generation of platelet concentrates by Choukroun et al. (2001). PRF is generated by slow gradual fibrin polymerization occurring during centrifugation. Such preparation of PRF does not require anticoagulants or activators. Therefore, the production of PRF is simpler, faster and cheaper than for platelet-rich plasma (PRP) (Dohan et al. 2006). The slower

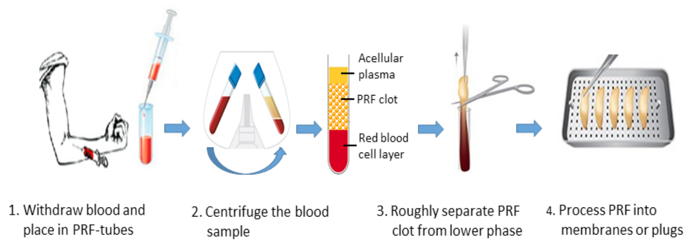

Image (created by C. Wolf-Brandstetter):
Basic principle of the preparation steps to obtain platelet rich fibrin (PRF)

and continuous release of platelet cytokines and growth factors after application is another advantage noticed in PRF over PRP (He et al. 2017). PRF consists of a fibrin matrix embedding platelets, leucocytes, circulating stem cells, cytokines, and variety of growth factors (Choukroun et al. 2006) resulting in substantially more leucocytes than in previous PRP preparations. Leucocytes as well as platelets represent important players in wound-healing processes (Adamson 2009). It is well known that these cell types are responsible for the activation and release of important biomolecules such as growth factors, in particular different types of platelet-derived growth factors (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor β1 (TGF-β1), but also coagulation factors, and cytokines, altogether capable to stimulate cell recruitment, proliferation, remodelling, and differentiation of the cells involved in wound healing process (Nurden 2011). The interaction between the cytokines and their supporting fibrin matrix was suggested to be most important in comparison to any other platelet derivatives, as free cytokines are rather rapidly degraded ...(continued on page 3)

Master thesis

Effect of platelet rich fibrin formulations on wound healing and bone regeneration after tooth extraction

Master of Science in Implantology and Dental Surgery - 2021

Objectives: This study aimed to investigate the efficacy of platelet rich fibrin (PRF) in post-extraction sockets in promoting wound healing (soft tissue healing, post-extraction pain and swelling), bone regeneration (vertical and horizontal alveolar ridge loss and bone formation ratio) and reducing the incidence of alveolar osteitis AO.

Material & methods: Search for respective studies was conducted on MEDLINE (via PubMed) till January 2021 adressing randomized or not randomized clinical trials that assessed effect of PRF formulations on wound healing and post-extraction morbidities in human sockets. The selection process yielded 25 studies published between 2013 and 2020. Considerable heterogeneity with respect to study setup or details in the assessment of outcome parameters was observed. Hence it was not meaningful to perform a meta-analysis for the majority of outcome parameters except for incidence of alveolar osteitis.

Results: The analysis of the studies shows a positive effect of PRF formulations on enhancing soft tissue healing, reducing post-extraction pain and swelling in the early healing phase up to one week. Regarding bone regeneration, a positive effect was observed after non-traumatic extraction in term of alveolar ridge preservation, however no positive effect was observed after surgical extraction. PRF was shown to be also effective in increasing new bone formation ratio after non-traumatic extraction. With respect to surgical intervention, no conclusions are possible yet. According to the pooled effect of the performed meta-analysis on incidence of alveolar osteitis, PRF reduced the risk factor of alveolar osteitis by 62%.

Conclusion: The present review suggests PRF application, whenever enhancing of wound healing and reduction post-extraction morbidities are needed. This review suggests also using PRF after removal of third molar in smoker patients to reduce AO development. PRF has a significant impact on alveolar ridge regeneration after non-traumatic extraction. Flap elevation seems to decrease or cancel this effect.

Key words: platelet-rich fibrin; tooth extraction; wound healing; alveolar ridge preservation; alveolar osteitis.

List of included studies

Afat, I.M. et al. (2018) Effects of Leukocyte- and Platelet-Rich Fibrin Alone and Combined With Hyaluronic Acid on Pain, Edema, and Trismus After Surgical Extraction of Impacted Mandibular Third Molars. J Oral Maxillofac Surg 76(5): 926-932

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Girish Kumar, N. et al. (2018). To assess the efficacy of socket plug technique using platelet rich fibrin with or without the use of bone substitute in alveolar ridge preservation: a prospective randomised controlled study. Oral and Maxillofacial Surgery, 22(2), pp.135–142.

Hauser, F. et al. (2013). Clinical and Histological Evaluation of Postextraction Platelet-rich Fibrin Socket Filling. Implant Dentistry, 22(3), pp.295–303.

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...with half-times of a few hours. PRF was used as a sole grafting material but was meanwhile combined with a variety of other bone grafts. Besides its application in the context of tooth extraction it was successfully adapted in many other indications such as periodontal defects, treatment of palatal clefts or open apexes.

According to its simplicity in preparation the number of publications increased massively over the years. However, the exact PRF preparation protocols were modified within the last decade and when looking into the very preparation details even seemingly identical protocols can differ in critical details as outlined further below. In the initial protocol the need of the application of high relative centrifugal forces (RCF) was reported. First protocols applied 3,000 rotations per minute (RPM) for 10 min, while meanwhile the actual standard protocol (S-PRF) is described by centrifugation at 2,700 RPM for 12 min. Further modifications focused on a more pronounced decrease of centrifugation force, resulting in one fourth of the RCF. The obtained preparation is part of the so called low speed centrifugation concept (LSCC) and was entitled as advanced PRF (A-PRF). Direct comparison of PRF obtained for standard vs. new protocols revealed a different distribution of cells within the forming clot, increasing the number of platelets and leukocytes in the A-PRF preparation (177 g; 1200 RPM; 8 min), with a more balanced distribution of cells within the matrix. A subsequent study by Kobayashi et al. (2016) focused on growth factor release in consequence of different preparation protocols and found more growth factors released from A-PRF compared to L-PRF, in particular at later time points up to 10 days. Within the last years, more detailed *in vitro* research was dedicated to details of the centrifugation process, specifically with respect to centrifugation force, centrifuge manufacturer and related vibrations as well as the type of used vials for blood collection/centrifugation.

One such protocol detail that lead to much confusion among published articles is the notation of actual centrifugation forces applied (the RCF-values), which have substantial impact on final PRF characteristics. Unfortunately, standard reporting of centrifugation protocol is presented in the majority of publications in RPM instead of the RCF-values and it might be guessed that many authors are not aware on the role of actual applied centrifugation force that can differ as much as twofold from original protocol when a completely different rotor size was used. A critical point in this aspect is, that many centrifuge manufacturers provide only RPM values on their centrifuges and calculation of actual applied values requires some effort.

The reader is referred to one article by Miron et al. (2018) elaborately explaining the difference between RPM and RCF and the typically chosen options to report the RCF. A concise summary of this specific topic you can find on page 4 of this issue.

The importance of one other critical aspect was elucidated only recently, namely the impact of the chemical properties of the used centrifugation tubes - also described in more detail on page 4. Such surface properties might affect onset of coagulation process or other specific sub-steps in coagulation cascade by different activation of the platelets as well as can lead to contaminations of the obtained PRF preparations. It is indeed important to note that the impact of the used tubes had much higher impact on size and weight of obtained clots than the used centrifuge type, when comparable g-forces were applied (Miron et al. 2020).

Two more PRF-protocols, deviating from above mentioned typical protocols, should be shortly introduced, too: A somewhat older protocol by Anitua et al. (2004) used sodium citrate as anticoagulant followed by a centrifugation step at 460 g for 8 min. Afterwards, the plasma fraction was collected and incubated at 37°C in the presence of calcium ions to start clot retraction. The second one was introduced as Sacco's method in 2010 (Massimo et al. 2010). Here, the blood is centrifuged using a specific centrifuge (Medifuge) with pre-set speed alterations. This protocol comprises different steps, starting with 2 min at 2,700 RPM, followed by 4 min at 2,400 RPM, again 4 min at 2,700 RPM and finally 3 min at 3,000 RPM. The combination of these different steps produces a compact fibrin matrix, being rich in growth factors. Such resulting grafts are also frequently entitled as "concentrated growth factor" (CGF) membranes as suggested by the manufacturer of the Medifuge. This leads to some more confusion, but such CGF preparations can be regarded as closely related to the standard protocol of PRF prepared at 2700 RPM at centrifuges with ~708 g. However, CGF preparation are rather seldom referred to in actual PRF publications.

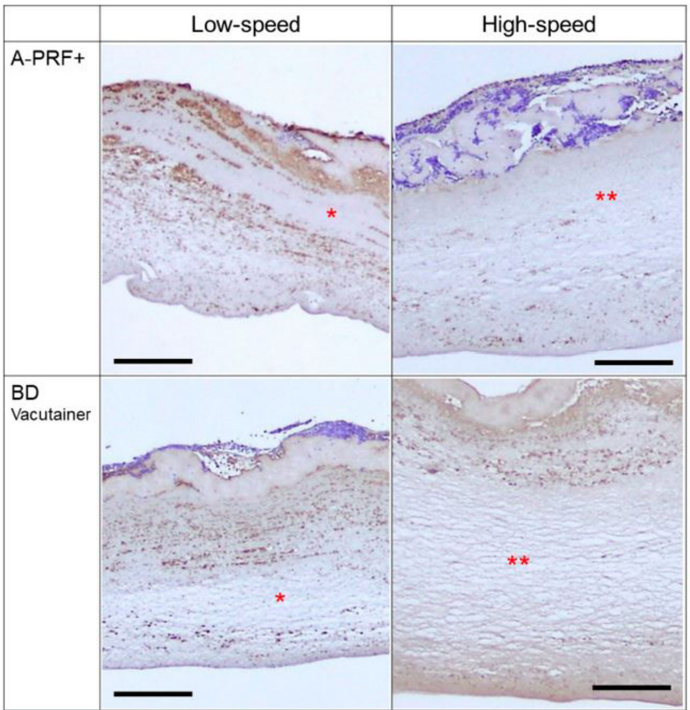


Image: Summary of platelet distribution under various conditions. Asterisks represent wide-open spaces, where platelets were distributed sparsely. Double asterisks represent wider spaces than single asterisks. Bar scales are 200 µm, from Tsujino et al. (2019) - free use CC-BY)

A study by Tsujino et al. (2019) using different tube types demonstrated that for the A-PRF protocol with lower centrifugal force platelets were distributed homogeneously within the PRF matrix regardless of tube types. In high-speed centrifugation (CGF-protocol), platelets were distributed mainly on one surface region of the PRF matrix in glass tubes, whereas in silica-coated tubes, platelet distribution was rather widely distributed (see Figure above). Further, it was concluded that high centrifugal forces might activate platelets to release their growth factors by activating leukocytes. Also Dohan Ehrenfest et al. (2012) suggested that the main problem with platelet concentration technologies is not the quantity of platelets, but the interplay between platelets, leukocytes, fibrin and growth factors.

It is not surprising that for data based on strikingly heterogenous protocols no clear recommendations could be obtained, although several reviews (Miron et al. 2017, Ghanaati et al. 2018, Dragonas et al. 2019, Xiang et al. 2019) aimed to increase the level of evidence. In our own meta-analysis we tried to solve the problem of heterogeneous protocol types by respective subanalyses. Unfortunately this was only possible for the aspect of centrifugation force, while specification of used tubes was often missing and many authors did not respond even when directly contacted. Nonetheless, only recently a German S3-guideline was published on benefit of PRF, further details can be found on page 5.

Specific important details in PRF preparation

Centrifugation

- Centrifugation is the central step in preparation of PRF. Many research groups have retranscribed centrifugation parameters over the last 20 years. Unfortunately, several authors have not regarded two important details - better to use relative g-forces by means of the RCF value (RCF = relative centrifugal force) instead or the speed (RPM = rounds per minute) and the specific location to which this g-force refers. One article by Miron et al. (2018) is specfically dedicated to this topic and related **misinterpretations.**

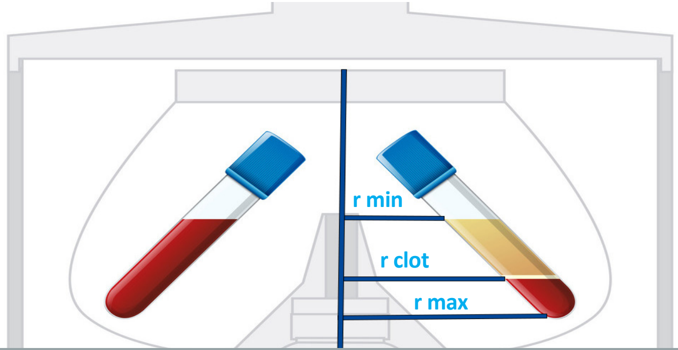


Image (created by C. Wolf-Brandstetter): The radius has impact on relative centrifugal force and respective values depend on the location at which relative centrifugal force is of interest: RCF = 11.18 x r x $(N/1000)^2$

- High-quality centrifuges can switch between RCF and RPM mode. It should be noted that the specified RCF according to international standards refers to the bottom of the tube (r_{max}). If the actual radius is known, the corresponding RCF values at different positions (see illustration above) can be easily calculated using the following formula: RCF = 11.18 x r x $(N/1000)^2$, where N is equal to RPM and r the radius in mm.
- The other important aspect refers to the **location** to which the RCF value refers. In first publication the orgiginal authors Choukroun et al. (2006) referenced their given value to the minimum position at the top of the centrifuge tube. Later a series of authors reported centrifugation with 400 g at the position of the clot. However, as the position of the clot formation depends strongly on centrifuge details, such as angulation of the rotor, this position cannot be identified in detail. Hence overall best solution is to report RFC values reference to the **bottom of the tube (r_{max}).** Most studies have an RCF-max value ranging from 559 g to 805 g, with a value of 708 g meanwhile established as a standard value.
- In our meta-analysis (Al-Badran et al. 2022) we specifically investigated if the use of different g-forces has an **impact on clinical outcomes**. As the reported protocol details were not always complete, no final decision was possible but there was strong evidence that for general healing in terms of soft tissue healing, pain and risk of alveolar osteitis the 2 protocols with intermediate g-forces - namely the standard protocol with 708 g and the so called concentrated growth factor (CGF) preparation - resulted in overall best outcomes.
- Dohan et al. (2018) demonstrated the impact of centrifuge **vibrations** on the vitality of retained cells, which was massively affected by the centrifuge type. In particular for protocols applying high RCF values such vibrations would play an even greater role and might explain the worse outcomes for PRF produced with more than 708 g (Al-Badran et al. 2022).

Impact of tube type

- When working with PRF, there is one very important fact to bear in mind. The effectiveness of the product depends primarily on the timely **onset of blood coagulation**, which has to correspond to the effect of gravity during the centrifugation step. Only if the fibrin network is formed at the right time will the desired cells be included in the forming network. Glass or coatings based on silica (SiO_2) particles are best initators of blood coagulation.
- Various recent studies show that the **choice of tubes** used is of extreme importance for the quality of the PRF product. Huge differences have been documented between tubes manufactured by different commercial suppliers, with up to **250% difference in clot size**, even when all centrifugation protocols were performed on the same machine with blood from the same patient and the same protocol.
- For a number of commercially available products (e.g. Neotube and Vacuette), silica microparticles were found in PRF preparations containing **5-30% silica microparticles** see Figure, depending on the tube brand. Tsujino et al. (2019) even demonstrated toxic effects on periosteal cells by adsorbing of such particles to the plasma membrane and inducing apoptosis.

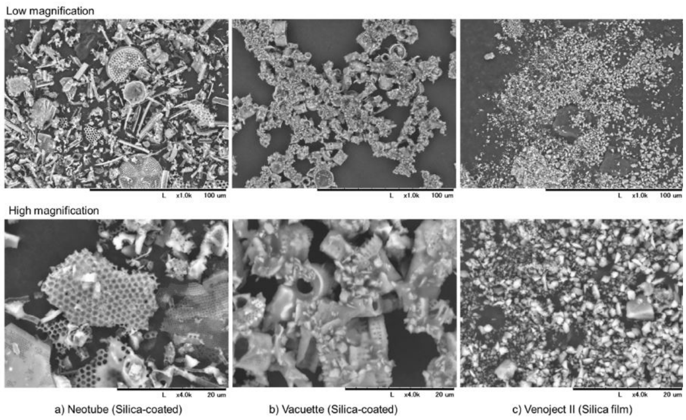


Image: Scanning electron microscopy (SEM) observations of silica microparticles contained in PRF clots produced in tubes of different manufacturers: (a) Neotube tubes (b) Vacuette tubes and (c) Venoject II tubes at different magnifications (from Tsujino et al. (2019) with permission)

- The data collected so far support the prediction that PRF preparations with silica-coated tubes could be toxic to the surrounding cells at the implantation site and reduce the therapeutic efficacy of PRF preparations. However, there have been no documented complaints of serious complications with the use of silica-containing PRF preparations. This is probably due to the efficient **degradation of silica** microparticles in the body by phagocytosis or extrusion.
- To avoid misunderstanding, it must be noted that **silica is different from silicone.** While silica is commonly used in the manufacturing of glass, silicone is a synthetic polymer created from the combination of silicon, oxygen, carbon, and/or hydrogen. Silicone is commonly used as sealant, but also as a coating of glass tubes. Excess silicone coating actually delays coagulation. Use of such tubes led to a drastic ~ 200% reduction in PRF clot sizes
- In conclusion overall best success was reported for the use of **glass tubes** which are approved for clinical use.

Miscelleanous

Equipment

High Quality Centrifuges

Image from www.a-prf.com

DUO Quattro
Duo Quattro is the new certified device (MD class II) based on Chokrouns original protocols and products. This machine can be obtained by the manufactorer or by several local suppliers. For more information visit: **www.a-prf.com**

Image from www.intra-lock.com

Intra-Spin
The IntraSpin system components are FDA-cleared and CE marked and are optimized to ensure proper material biocompatibility and clinical performance. It is the most widely used system in PRF related publications. (see: **www.intra-lock.com/IntraSpin**)

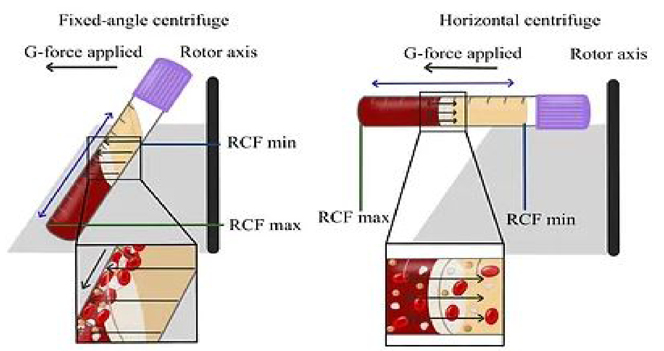


Image from www.nextgenbiomaterials.com

Bio PRF Centrifuge
The Bio-PRF BF-1 system is the first commercially available horizontal centrifuge for the production of PRF. While on a fixed-angle centrifuge, the blood cells accumulate mostly on the back walls of tubes, the cells separate here much more efficiently throughout the entire tubes. (see: **www.nextgenbiomaterials.com**)

EBA 200 (Hettich)
This centrifuge is not that well known as the other PRF centrifuges but is also available as **certified medical device** and was used in several clinical studies, resulting in high qualitsy preparations (also cited in our meta-analysis).

Required tubes

Note: although some concerns arose form the use of silica coated plastic, this type of tubes is still the typically sold option for solid PRF. The use of approved suppliers is recommended!

- Sets for different applications are provided by PRF process (glass for A-PRF, silica coated plastic and specific plastic tubes for liquid PRF). See: **www.a-prf.com**
  Respective approved tubes corresponding to Choukrouns tubes are also supplied worldwide by different distributors
- Corresponding tubes for the Inta-Spin system are provided on the website of the manufacturer, tubes for solid PRF are again based on slica coated tubes, but these are certified. See: **www.intra-lock.com/IntraSpin**
- Plain glass tube without any additives (red tubes) as well blue tubes for liquid PRF fitting to the BIO PRF centrifuge are available at **bio-prf.com/products/**

Tips and Tricks

- After the usual preparation of the puncture site (ideally the median cubital vein in the crook of the elbow), a butterfly needle is inserted into the vein at an angle of 30°. Once the vein has been hit, the angle should be flattened. The blood can then be collected easily into vacuum tubes.
- To avoid coagulation before centrifugation, the PRF tubes must be centrifuged **as quickly as possible**. When loading the centrifuge, it is essential to ensure that there is no imbalance, i.e. that the weight of the tubes placed exactly opposite each other is identical.
- After centrifugation, **two phases** are recognizable: a lower red phase containing mainly erythrocytes and an upper PRF phase. To separate the **solid PRF** (glass tubes and high centrifugation force) matrix from the lower red phase, it is advisable to first **roughly separate** the two phases using scissors. To do this, carefully grasp the solid upper PRF phase with sterile tweezers, lift it up and roughly separate the two phases in the upper area of the red phase and transfer the PRF into a PRF box. The remaining red phase can now be carefully removed from this box using a blunt instrument. Depending on the indication, solid PRF matrices can then be further processed either in a **PRF plug** or in a **thinly pressed PRF matrix**.
- If **plastic tubes** are used instead of glass, the two phases of the blood are initially liquid. **Liquid PRF** can be ideally combined with bone substitute materials. The still liquid PRF (upper phase) is carefully removed from the remaining red lower phase using a syringe. A 5 ml syringe with a long and wide cannula with a size of 21 gauge is best suited for this step. It is advisable to tilt the tube slightly in order to better recognize the boundary between the two phases and to be able to remove as much liquid PRF as possible.

Guideline

In 2022, a German S3 guideline (valid until 2027) on various applications of PRF was published, in which all relevant data forming the basis for the recommendations were extracted and included in corresponding tables.
The long version is freely available, but only in German.
Leading specialist societies for this guideline were:
German Society for Implantology in the Dental, Oral and Maxillofacial Area (DGI) and German Society for Dental, Oral and Maxillofacial Medicine (DGZMK)

AWMF registration number: 083-042

This guideline deals with the question of the clinical efficacy of PRF in the following indications:
- Socket/ridge preservation
- Sinus floor elevation
- Lateral augmentation
- Vertical augmentation
- Three-dimensional augmentation
- Peri-implant diseases
- Immediate implantation

Spontaneous wound healing is considered as a reasonable control group when PRF is used as the sole therapy. When combining PRF with other bone graft substitutes or membranes, the reasonable control group should be the same treatment procedure using the same bone graft substitutes/membranes without PRF. This approach allows the clinical efficacy of PRF to be investigated while minimizing other confounding factors.

Concise summary:

- Recommendation 1:
  Filling the socket with solid PRF plug matrix leads to improved **socket healing** and can be recommended for open healing sockets.
  Vote: 32/0/2 (yes, no, abstention) with strong consent
- Recommendation 2:
  The sole use of solid PRF plug matrix to fill the socket contributes to **volume preservation of the alveolar ridge** and can be recommended as an alternative treatment option if socket/ridge preservation is indicated.
  Vote: 32/0/2 (yes, no, abstention) with strong consent

  For the use of PRF with or without bone substitutes for other specific indications no statements or treatment recommendations could be made based on the current data situation:

- Pain - high risk of bias (no blinding of patients in many studies)
- Sinus floor elevation - high risk of bias, low number of patients
- Lateral augmentation - too low number of available studies
- Vertical augmentation and three-dimensional augmentation - no studies at all
- Immediate implantation - high risk of bias (blinding of investigators), low number of patients,
- Peri-implant diseases - only 1 study with high risk of bias (no blinding of investigators), low number of patients

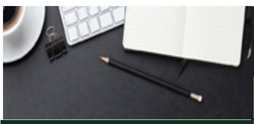
For a variety of above mentioned applications a few promising data were pubslihed but more high quality studies are needed for final decisions or recommendations.

Save the date

International congresses:

- **AEEDC Conference**: February 6-8, 2024 | Dubai, UAE
- **Pacific Dental Conference:** March 7-10, 2024 | Vancouver, Canada
- **Ontario Dental Association** Annual Spring Meeting: April 18-20, 2024 | Toronto, ON, Canada
- **AAO Annual Session:** May 3-6, 2024 |New Orleans, LA, USA
- **ITI World Symposium:** May 9-13, 2024 | Singapore
- **Dental Bern:** June 6-8, 2024 | Bern, Swiss
- **99th European Orthodontic Society Congress**: June 9-13, 2024 | Athens, Greece
- **IFEA WEC** - World Endodontic Conference: September 11-14, 2024 | Glasgow, Scotland, UK
- **World Dental Congress**: September 12-15, 2024 in Istanbul
  The World Dental Congress is a flagship continuing-education event for FDI

On our OREC platform we present again a series of Online Live Lectures (see selection below), that can be watched live or as video on demand at any later time point. For booking any of these courses or access to the library please visit our website at imc-orec.de.



Online-Courses	Topic	Date (EN)
	Premedication and pain control (Dr. Schuon)	3 January
	Apical root resection (Prof. Weisscher)	20 February
	Impression techniques and soft tissue management (Dr. Frashieri)	7 March
	Principle of tooth movement (Dr. Keil)	22 May

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