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Perspective

L-PRF for Use in Oro-Maxillo-Facial Surgeries: *What Do We Know?*

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Précis - The art and science of oro-maxillo-facial reconstruction is of great interest for contemporary oral and maxillofacial surgeons; in search for better bioengineering strategies and biomaterials: a core driver for bio-dental research, today. Leukocyte and *Platelet-Rich Fibrin (L-PRF) is a 3-D autogenous biomaterial obtained via the simple and rapid centrifugation of whole blood patient samples, in the absence of anti-coagulants, bovine thrombin, additives or any gelifying agents. A relatively new "revolutionary" step in 2nd generation platelet concentrate-based therapeutics, the clinical safety, and more so, efficacy and effectiveness of L-PRF remains highly debatable, whether due to significant variabilities in preparation protocols, limited evidence-based scientific and clinical literature and/or inadequate understanding of its bio-components.*

Despite significant improvements, our current clinical armamentarium, strategies, procedures and approaches used to reconstruct and heal complex oro-dental and maxillo-facial defects, including different bone grafting methods are deemed restricted, daily. Often *multi-factorial*; whether due to limited self-renewal capacity of the defect and/or limited donor supply, increased morbidity, risk of antigenicity and foreign body reactions, associated with the grafts used. Operative associated time and cost contribute as well. Regenerative tissue engineering directs the ongoing development of *novel* biomaterials for use in oro-dental surgery; alveolar bone regeneration and repair, is a fine example. Localized site development, sinus lift and socket preservation, are others.[2] The family and sub-families of *'Platelet Concentrates'* are certainly incessantly promising.

Briefly, Platelet Concentrates (PCs) are autologous blood extracts obtained through centrifugation of whole blood samples. The preparation procedure allows the gathering and concentration of platelets and other therapeutic blood constituents (fibrinogen/fibrin, growth factors, leukocytes and circulating cells), in clinically usable preparations (surgical adjuvants), which may promote hard and soft tissue wound healing and regeneration.[3]

Despite promising clinical observations, overall effectiveness remains debatable mostly due to mixed and variable clinical outcomes, limited high-quality evidence-based literature, and poor characterization of end-products and preparation protocols; and - until recently - lack of proper terminology systems to classify such preparations. Indeed, to the best of our knowledge, the first consensus appeared in 2009, describing four PC sub-families, based on extant or hypothesized variability in biological content (fibrin/cell), properties (gelification, for example) and potential applications: Pure Platelet-Rich Plasma (P-PRP), Leukocyte and Platelet-Rich Plasma (L-PRP), Pure Platelet-Rich Fibrin (P-PRF) and Leukocyte and Platelet-Rich Fibrin (L-PRF).[4] Today, the *L-PRF sub-family*[2-4] is receiving utmost attention, due to simplicity, malleability

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and probable cost-effectiveness; a revolutionary dynamic novelty in contemporary oro-maxillo-facial tissue repair and regeneration.

L-PRF is an autologous platelet concentrate of whole venous blood.[4,5] A slowly- and strongly-polymerized fibrin gel rich in growth factors, platelets, leukocytes (almost half of the initial blood harvest) and lymphocytes, is collected following simple and rapid (~10 minutes) centrifugation of blood in vacutainer tubes, without anti-coagulant, bovine thrombin, additives or any other gelifying agent (*i.e.* under naturally physiological concentrations of autologous thrombin). Preparation protocols vary, recommendations for reproducibility are provided in Figure 1. The gathered clot (or biomaterial) is stable, resilient, strong, adhesive and malleable, and it can be cut or adapted into different anatomical defects and applications: used directly as filling material, mixed with bone grating material, or compressed into a strong fibrin membrane. Alongside this established clinical ease of use and handling, the biochemical composition of the L-PRF by-products provides it, up to an extent, with attractive hemostatic, angiogenic, osteogenic, anti-inflammatory, anti-microbial, pain-inhibitory and wound healing characteristics;[4-8] an open-ended topic of ongoing debate in the scientific and clinical community worldwide.[6-9] Indeed, despite promises, the accumulating *in vitro* and *in vivo* results regarding soft- and hard-tissue regeneration, have been fueling controversies especially regarding the "real extent" of clinical effects/effectiveness and continues to be the matter of vigorous debate due to key biological and technological issues.

There is a need to address such questions and concerns, with prospective long-term post-operative evaluation of L-PRF use, from high-quality Randomized and Controlled Clinical Trials, and not solely from in vitro, in vivo and case report studies.

Most prominent L-PRF applications in the literature include the treatment of periodontal intra-bony defects (with or without open flap, *versus* de-mineralized freeze-dried bone allografts or Bio-Oss® constructs, for example); treatment of furcation defects (*versus*. open flap debridement, for grade II mandibular defects); treatment of Miller Class I/II gingival recessions (*versus* coronally-advanced flaps, connective tissue grafts or sub-epithelial connective tissue grafts); and sinus floor augmentation procedures (lateral osteotomy window *versus* using an absorbable covering membrane, such as Geistlich Bio-Gide®). With a snowballing sum of studies (case reports/series, mostly), it is challenging for clinicians and researchers to obtain the "bottom line" on the "real" benefits of L-PRF. Crucial data about L-PRF preparation and characterization are often forgotten or omitted. Increasing indication of intrinsic centrifuge characteristics (*i.e.* vibration) pointedly impact the biomaterial's composition/architecture, cytokine release kinetics and cell integrity/viability;[8,9] key variables requiring proper documentation in future publications.

With several "new" and "revolutionary" centrifuges and kits being continuously developed and commercialized under confusing or mystifying "PRF-related" labels, basic characterization of tested "PRF" preparations (*i.e.* histology and SEM analysis) should be encouraged as "minimum

Figure 1. Contemporary Recommendations for L-PRF Clinical Preparation Protocol

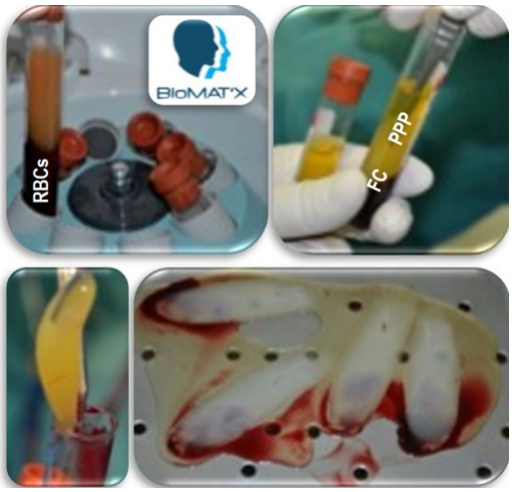
For the most reproducible and clinically-usable L-PRF clots and membranes, and for the best possible clinical outcome, the following protocol is recommended:

Collect a 5-9mL whole venous blood sample into 2-3 sterile 6mL glass-coated plastic vacutainer tubes (without anti-coagulant).

Centrifuge immediately for 10-12 minutes at 2700/3000 revolutions per minutes (rpm) using a high-quality table centrifuge.

Collect L-PRF clot carefully from the middle portion of the tubes. Typically, three phases should be evident in the tube. **UPPER:** straw-colored acellular plasma (PPP), **MIDDLE:** yellowish fibrin clot (FC); and **LOWER:** red-colored lower fraction containing red blood cells (RBCs). Remove the upper layer in order to collect the middle fraction: 2mm below the lower dividing line.

The collected clot can then be used directly as filling material, mixed with bone grating material (L-PRF plug/block) or compressed into a stong L-PRF membrane, using a surgical box designed to prepare it without damage.



REMINDER: Quick handling is critical in order to obtain bioactive L-PRF clots charged with serum and platelets.

criteria" to assess the final product and preparation quality. In this context, Choukroun's "original" L-PRF (5-10mL whole blood centrifuged at 2700-3000rpm or 400g for 10-12 minutes) *should* be considered the "current gold-standard" preparation, a validated protocol.[10] Recent publication of the first detailed clinical "Step-by-Step" guide-line useful for L-PRF (https://kuleuvencongres.be/ENHD2018) supports the aforementioned protocol and indeed encourages its implementation in future clinical trials. Because of hype, readers should be aware of probable publication bias within the L-PRF literature, as studies reporting "significant" benefits or effects are far more likely to be published than those with modest or no results. Quality of reporting of RCTs does not necessarily describe the value of L-PRF use, especially since most of reviewed literature report *some* benefit in early wound healing, bone formation/maturation and post-surgical pain inhibition or control. [6,9]

Now, L-PRF may still be designated as an innovative tool for contemporary oro-maxillo-facial tissue reconstruction and bioengineering. While existing reports suggest that L-PRF improves early wound healing and promotes post-surgical bone formation/maturation, it is noteworthy that a clearer consensus seems present regarding its significant beneficial impact on post-surgical pain and discomfort control, regardless of the type of procedure.[6,9,10] In a *pilot* prospective observational study[9] involving a cohort of 11 patients receiving a Wilcko's modified periodontally accelerated osteogenic orthodontics – *a surgical procedure which allows faster tooth movement by combining orthodontic forces with corticotomy and grafting of alveolar bone plates* – technique with L-PRF, accelerated wound healing with no signs of infection or adverse reactions. Post-surgical pain, inflammation and infection were recorded for 10 days post-operatively, while the overall orthodontic treatment and post-treatment stability were followed up to 2 years. Interestingly, our data analysis revealed complete resolution achieved in all patients by day 8, average orthodontic treatment time calculated at 9.3 months and all cases were stable throughout. Thus, it was concluded that combining L-PRF (within the graft and as a covering membrane) with traditional bone grafts (L-PRF plug/block) accelerates wound healing and reduces post-surgical pain, inflammation, edema, and infection without interfering with tooth movement or post-orthodontic stability, over an extended two-year period, thereby alleviating the need for analgesics and anti-inflammatory medications.

It is useful to re-emphasize that new L-PRF preparations, unlike its predecessors, tend to function more as biologically-active biomaterials/scaffolds for autologous cells and growth factors delivery; a "living tissue" preparation for natural guided tissue regeneration and not simply a "growth factor-rich" surgical adjuvant.

This remains an un-explored territory in dental bioengineering research, and better RCTs are needed to confirm the reported *"clinical observations"*, whilst other scientific studies are awaited to properly characterize or elucidate the underlying mechanism(s) of action, from the physical, chemico-biological and mechanico-rheological aspects of L-PRF, for a more practical understanding for its use and application.

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