Open Access Journal of Surgery

Juniper Publishers key to the Researchers

Mini Review
Volume 2 Issue 4 – March 2017
DOI: 10.19080/OAJS.2017.02.555593

Open Access J Surg


# Overview and Future of Hemo-Components and Natural Guided Regeneration

**Andrea Mascolo[1] and Elio Boschetti[1,2]**

[1]*Ludes Foundation HEI, Malta*

[2]*Institute of Dentistry, University of Cagliari, Italy*

**Submission:** February 28, 2017; **Published:** March 03, 2017

***Corresponding author**: Andrea Mascolo, Associate Professor of Dental Medicine, LUDES Foundation HEI Malta, Email: andrea.mascolo@ludes.edu.mt

**Abbreviations:** PRP: Platelet-Rich Plasma; PRF: Platelet-Rich Fibrin; P-PRP: Pure Platelet-Rich Plasma; PRGF: Plasma Rich in Growth Factors; L-PRP: Leukocyte-and Platelet-Rich Plasma; P-PRF: Pure Platelet-Rich Fibrin

## Mini Review

The History of Platelet Rich Fibrin (hemocomponents) started in 1970, when Matras described a fibrin glue, formed by polymerizing fibrinogen with thrombin and calcium, which was used to improve skin wound healing in a rat model in 1970 [1]. Because of the low concentration of fibrinogen in plasma, the stability and quality of fibrin glue were low. A few years later several research works proposed an upgraded concept for the use of blood extracts, termed "platelet-fibrinogen-thrombin mixtures" or "gelatin platelet - gel foam" [2,3]. In this new concept, the fibrin glues were presenting a significant concentration of platelets within the final preparation. The idea was first to reinforce naturally the fibrin gel, and also to combine the healing properties of the platelets with those of the fibrin. This improvement allowed to prepare more natural products, integrating more natural blood constituents as it should.

These products were the first platelet-rich plasma gels. These new strategies insisted in the role of platelets within the fibrin gel, and offered excellent preliminary results in ophthalmology, neurosurgery and general surgery. Whitman proceeded to develop this technique in 1997 and particularly Marx et al. [4,5] in 1998. The Leukocyte- and Platelet-Rich Fibrin L-PRF clot was often described as "optimized blood clot" that can be surgically handled and used. The rationale to use this glue/membrane and its success is due to fibrin, platelets, growth factors slow release, leukocytes and other cells: all these components are the key active actors of the natural healing process and combined together are forming a kind of engineered tissue extracted from the blood circulating tissue [6].

Unfortunately at the moment there is a lack of an international standard for characterization, classification and identification of surfaces in implantable materials [7,8], in particular a standardization is needed to obtain an optimal and reproducible results, however the current classification of platelet-rich concentrates is based on their fibrin architecture and cell content. It consists in two main groups of products, platelet-rich plasma (PRP) and platelet-rich Fibrin (PRF), both of which are available in a pure or leukocyte-enriched form (L-PRP and L-PRF) [9]. Each product has an unique biological profile that dictates its clinical applications. L-PRF concentrates provide slow release of many growth factors and can be easily prepared during surgery [10-14]. They are inexpensive and autologous; therefore, they avoid the complications associated with allogenic blood use.

Pure Platelet-Rich Plasma (P-PRP) products are preparations without leukocytes and with a low density fibrin network after activation. One largely advertised method of P-PRP is known under the commercial name PRGF [Plasma Rich in Growth Factors or Preparations Rich in Growth Factors or EndoRet, Biotechnology Institute BTI (dental implant company), Vitoria, Spain] and was tested in many clinical situations, particularly in sports medicine. P-PRP gel released most of its growth factors in the first hours and completely dissolved in the medium after 3 days, even after a maximum artificial fibrin polymerization.

Leukocyte-and Platelet-Rich Plasma (L-PRP) products are preparations with leukocytes and with a low-density fibrin network after activation. The methods to prepare the PRP

membranes require two or one centrifugations, there are, infact, some new faster machines like Arthrex ACP®, nevertheless an anticoagulant is always needed. PRP families are not adapted (complicated, expensive, with mixed clinical relevance) for daily oral applications. PRP families are substitutions to fibrin glues in most other surgeries, particularly to improve skin wound healing. The use of gelling of the PRP on the surgical site makes it adequate surgical adjuvants in many clinical situations, even if the exact effects - in comparison to fibrin glues - remain largely debated.

The PRP solutions have also the advantage to be liquid before activation, and can therefore be used as injection or placed during gelling on a skin wound or suture (similar to the use of fibrin glues) in various sports medicine or orthopedic applications. In this strategy of regenerative medicine, the platelet suspensions are injected like other pharmaceutical preparations. The results of this method remain however largely debated in the literature, probably because of the large quantity of different protocols [14-16]. Pure Platelet-Rich Fibrin (P-PRF) - or Leukocyte- Poor Platelet- Rich Fibrin preparations without leukocytes and with a high-density fibrin network. These products only exist in a strongly activated gel form, and cannot be injected or used like traditional fibrin glues. However, because of their strong fibrin matrix, they can be handled like a real solid material for other applications.

L-PRF membrane remains solid and intact after 7 days and relases continuously a large quantity of growth factors, a significant part of it being produced by the cell population within the membrane. L-PRF family fits the needs of the applications in oral and maxillofacial surgery, as L-PRF clots and membranes present a volume and shape easy to combine with most surgical techniques, as filling and interposition healing biomaterial or as protection healing membrane. The fibrin architecture of L-PRF is constitued by connected trimolecular junctions, due to a slow polymerization of the platelet concentrate and due to the absence of heterologous thrombin. The results of this process is a flexible fibrin network, able to promote the gradual release of growth factors and leukocytes migrationduring extended period.

It is easy to prepare in large quantity and inexpensive, what makes it particularly adapted for daily clinical practice. PRF families in general are usable in other disciplines with interesting results, particularly for the treatment of skin chronic wounds and ulcers. The methods to prepare PRF never require an anticoagulant and a lower G-force is needed (around 400G). PRF products cannot be used as injectable products in sports medicine for example [12,17]. Some groups advocated that the presence of leukocytes may be negative for the therapeutic outcome, due to a potential risk of stimulation of the inflammatory process after the membrane placement in a wounded site [18]. Other researchers insisted on the need of some leukocyte population in the injectable PRP in order to increase the growth factors production, the release of anti-pain mediators and the natural anti-infectious activity.

Some kind of leukocytes, lymphocytes in particular, are playing a key function as regulation turntable of the healing and inflammatory process, and there is no reason to discard them. Leukocytes are not only inflammatory cells: they also present anti-nociceptive effects through different chemokines, anti-inflammatory cytokines (IL-4, IL-10 and IL-13) and opioid peptides (b-endorphin, metenkephalin, and dynorphin-A) and can therefore promote a clinically relevant inhibition of pathological pain [19-21]. The classification previously described is the only nomenclature which considers all forms of platelet concentrates for surgical use. However, other classifications systems were proposed in the recent years, but are limited because they only refer to Platelet-Rich Plasma products and sports medicine applications. Both proposals are not significantly evidence-based and do not allow to improve the current terminology [22].

Most publications about growth factors and platelet concentrations showed the relative lack of significance of these parameters, due to the many inter-individual variations and the short-term effects of these parameters: platelets being activated and active during a very short time and the growth factors being released, consumed locally or dissolved in the blood circulation in few minutes or hours after their release [23,24]. Platelet concentrates for surgical use are a system of all blood elements within a logical healing platform including the fibrin matrix, the platelets, the mediators and the cells all together to reach a clear and reproducible clinical result [25]. Castro in a systematic review founded favorable effects on hard and soft tissue healing and postoperative discomfort reduction were often reported when L-PRF was used, nevertheless, they found a lack of standardization of the protocol in regenerative procedure [26].

Temmerman et al. [27] compared bone ridge preservation L-PRF socket filling and natural healing following tooth extraction after 3 months; the results showed the use of L-PRF as a socket filling material in order to achieve ridge preservation is beneficial for all parameters considered (vertical height changes, width reduction, mineralized bone) during a 3 month observation period. Furthermore, the use of L-PRF results in less post-operative discomfort and pain for the patients. Multiple surgical specialties have recognized the potential advanatges of platelet-rich concentrates. Their use has been described in ophthalmology, neurosurgery, general surgery [22] orthopedic surgery, sports medicine [28] and oral and maxillofacial surgery [29]. Several applications of L-PRF concentrate have been described in the literature including postoperative hand wound healing yielding faster re-epithelialization and in the treatment of androgenic alopecia diminishing hair loss among others [30-32].

The role of L-PRF in endoscopic endonasal skull base surgery defect reconstruction was investigated by Soldatova et al. [33] who demonstrated the potential benefits of L-PRF membranes for the reconstruction of skull base defects with encouraging rate of healing progression as measured by the crusting score.


How to cite this article: Mascolo A, Boschetti E, Overview and Future of Hemo-Components and Natural Guided Regeneration. Open Access J Surg. 2017; 2(4): 555593. DOI: 10.19080/OAJS.2017.02.555593.

During the lasts years the production of platelet concentrates for surgical use from the PRF (Platelet-Rich Fibrin) family are becoming very popular in some surgical fields. The main product is classified as L-PRF and is used in oral and maxillofacial applications in particular. Many systems are available on the global market, but only one system to date is duly CE-marked and FDA-cleared (Intra-Spin System, Intra-Lock, Boca-Raton, FL, USA) [34].

The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors and fibrin architecture of L-PRF was investigated comparing 4 different centrifuges. The results showed significant differences in the vibrations level at each rotational speed between the 4 tested machines. The CE-marked and FDA-cleared device was the most stable machine in all configurations and it remains under the threshold of resonance, unlike the 3 other tested machines [35]. In another study M.F-Kobayashi demonstrated in vitro that reducing the centrifugation speed favored an increase in growth factor release from PRF clots which in turn may directly influence tissue regeneration by increasing fibroblast migration, proliferation and collagen mRNA levels [36].

## Conclusion

L-PRF treatment offers additional advantages: favorable effects on hard and soft tissue healing, postoperative discomfort reduction, simple harvesting, simplicity in use, no need for primary closure, and no risk for early membrane exposure. The economic implication in the final cost of a treatment has also to be taken into consideration. The vitro and molecular biology studies are very useful to understand which molecules are present in the clot and to hypothesize their role in the healing and regenerative process, however more clinical standardized studies are needed to demonstrate the quantity of growth factor is actually necessary to significantly improve the regenerative processes. Literature's results are often discordant, several practitioners report different clinical experiences and mixed clinical outcomes. These unpleasant facts are due to a chaotic market and a lack of standardization of the procedure. Further researches and clinical trial under a rigid protocol are needed to fully understand the potential and optimal effect of L-PRF in regenerative procedures.

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**How to cite this article:** Mascolo A, Boschetti E, Overview and Future of Hemo-Components and Natural Guided Regeneration. Open Access J Surg. 2017; 2(4): 555593. DOI: 10.19080/OAJS.2017.02.555593.

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**DOI:** 10.19080/OAJS.2017.02.555593




**How to cite this article:** Mascolo A, Boschetti E, Overview and Future of Hemo-Components and Natural Guided Regeneration. Open Access J Surg. 2017; 2(4): 555593. DOI: 10.19080/OAJS.2017.02.555593.