

Special Review: Consensus Conference

Guidelines for the publication of articles related to platelet concentrates (Platelet-Rich Plasma - PRP, or Platelet-Rich Fibrin - PRF): the international classification of the POSEIDO

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Abstract

Platelet concentrates for surgical use are autogenous regenerative preparations, produced by the centrifugation of the patient own blood sample. Most techniques are often regrouped inappropriately under the historical term of Platelet-Rich Plasma (PRP). Since 15 years, their use dramatically increased in many surgical fields, particularly in oral and maxillofacial surgery. The literature on this topic is considerable, but the published results are often contradictory. It is very difficult to sort and interpret the available data, due to a large number of preparation techniques, terminologies and forms of these materials, and the endless list of potential applications. This consensus conference of the Periodontology, Oral Surgery, Esthetic and Implant Dentistry Organization (POSEIDO) was established to support a classification system of these products, in order to improve and clarify the publications on this topic. Four main families of preparations can be defined, depending on their cell content and fibrin architecture: Pure Platelet-Rich Plasma (P-PRP), such as cell separator PRP, Vivostat PRF, PRGF-Endoret or E-PRP; Leukocyte- and Platelet-Rich Plasma (L-PRP), such as Curasan, Regen, Plateltex, SmartPreP, PCCS, Magellan or GPS PRP; Pure Platelet-Rich Fibrin (P-PRF), such as Fibrinet; and Leukocyte- and Platelet-Rich Fibrin (L-PRF), such as Titanium-prepared PRF and Intra-Spin L-PRF System. P-PRP and L-PRP exist in an inactivated liquid form, and can be activated and transformed respectively into a P-PRP gel and a L-PRP gel. This terminology will serve as a basis for future works to be published in the POSEIDO journal and as a first step for further research on the topic.

Keywords. Fibrin, fibrin tissue adhesive, Platelet-Rich Plasma, platelet, leukocyte.

1. What are platelet concentrates for surgical use?

Platelet concentrates for surgical use are autogenous products prepared through the centrifugation of a blood sample of the patient [1]. The concept of these technologies is to collect and gather the most active components from the blood sample - platelets (rich in growth factors), fibrin and sometimes leukocytes - and to prepare them in a clinically usable form. These preparations can be solutions or gels and can be injected or placed in a surgical site, on a wound or in an injured area, in order to regenerate the damaged tissues [2,3].

In most of these techniques, blood is collected with anticoagulant and then processed following a 2-step centrifugation [4]. The first step of centrifugation is used to separate the blood in 3 layers following a gradient depending on their weight: red blood cells at the bottom of the tube, acellular plasma (called platelet-poor plasma, PPP) at the top of the tube, and a whitish layer (sometimes called buffy coat, like in transfusion science) rich in platelets and cells between the 2 other layers. The red blood cells are then discarded and the second step of centrifugation is used to collect only this buffy coat and some acellular plasma. The final liquid platelet suspension is called Platelet-Rich Plasma (PRP) in transfusion medicine, and the term was used to regroup the many families of platelet concentrates for surgical use [1].

This platelet suspension can be injected in an injured site (for example in tendons or articulations in sport medicine)[5,6] or activated with bovine thrombin (or calcium chloride, or equivalent platelet activator)[7,8]. The activation of the suspension provokes the platelet growth factors release and the polymerization of fibrinogen into fibrin, to form a platelet gel similar to a fibrin glue that can be used on a surgical site or a wound [9]. This is the general description of the production of platelet concentrates, but many variations of the production exist. Particularly for the subfamily called Leukocyte- and Platelet-Rich Fibrin (L-PRF), blood is taken without anticoagulant, processed with a one step centrifugation and no platelet activator is needed [10].

The philosophy of these treatments is in fact to concentrate and use the positive effects of the actors of the coagulation process. Platelets, fibrin and leukocytes act naturally in synergy in order to promote the wound healing and tissue regeneration, and the concept of platelet concentrates for surgical use is to multiply this coagulation/regeneration effect on a surgical site or wound. In the history of these techniques, researchers have focused alternately on the fibrin matrix, the platelets, the growth factors and more recently on the leukocytes and circulating stem cells [3], and the terminology of these materials has evolved following these trends [11].

2. History of the terminology

2.1. Early history

The history of these technologies starts in fact with the fibrin adhesives developed more than 40 years ago [12]. The need of surgical adjuvants in order to improve healing and control diffuse bleeding promotes the development of fibrin glues. As first matrix of coagulation, fibrin is indeed a key element of the healing process, and these glues are still used nowadays [13].

In a second time, some researchers tried to improve their fibrin adhesives preparations by combining it with the other natural key actors of coagulation. These autologous preparations were termed « platelet-fibrinogen-thrombin mixtures » and were used with success in ophthalmology [14,15], general surgery [16] and neurosurgery [17].

Other authors called it « gelatin platelet (gel foam) » [18]. In these applications, these new preparations were used as fibrin tissue adhesives and the role of the platelets was advocated to serve only to reinforce the fibrin matrix architecture. The presence of platelet growth factors and the potential direct healing properties were not advocated or even considered.

It took several more years before the concept evolved and these preparations were considered to have direct healing properties. In 1986, Knighton et al. [19] developed an efficient clinical application for the treatment of chronic non-healing cutaneous ulcers, using a preparation using a 2-step centrifugation procedure and named “platelet-derived wound healing factors” (PDWHF). In other articles in 1988 and 1990 [20,21], the same technique was named “platelet-derived wound healing formula (PDWHF)”. In that time, the term “platelet-rich plasma” was only used as a technical term and was not the name of the final usable product. A few years later, Whitman et al. [22] published their clinical results in oral and maxillofacial surgery, using a platelet concentrate termed “platelet gel”.

2.2. PRP and the craze for growth factors

The craze for “growth factors” and the use of the term “Platelet-Rich Plasma” (PRP) really started with the article of Marx et al. in 1998 [7], in a study about the effect of a platelet-rich preparation during maxillofacial bone reconstruction. The platelet suspension was then activated into a gel using bovine thrombin. The use of the term PRP by these authors was in that time quite correct, as the preparation was produced using a cell separator from the hematology laboratory (and therefore was similar to a PRP used for transfusion). The “platelet-rich plasma (PRP)” term was initially developed in 1954 by Kingsley to designate thrombocyte concentrate [23], used for the treatment of patients suffering from severe thrombopenia.

After this article, the term of PRP – associated with the concept of growth factors - widespread and soon was used to name all kinds of preparations and techniques [24,25]. A huge number of new experimental or commercial techniques were proposed during the last 15 years [26-31]. This is at this time that started a significant confusion in the literature, as in most articles about platelet concentrates, many different protocols (commercially available or “home-made”) were tested under the name “PRP”, but in most cases without a proper characterization of the content and architecture of the tested concentrates [32]. Moreover, as the concept of “regeneration through growth factors” seduced many authors [33-35], the key role of the fibrin was almost completely neglected during many years, as if 30 years of research in fibrin-based surgical adjuvants had almost not existed.

As a result, even if these PRPs were largely investigated in vitro and in vivo in many applications, the literature is very contradictory and controversial, and the data are difficult to sort and interpret. In dentistry, it led to the general feeling that PRPs are not so useful [24,25]. After the initial craze, dental clinicians using these PRP preparations in their daily practice became very scarce.

2.3. Leukocyte- and Platelet-Rich Fibrin (L-PRF)

In parallel of the PRP history, a second family of materials initially called Platelet-Rich Fibrin was developed a few years later [10], and started to replace the PRP in oral and maxillofacial surgery. In this simple technique, blood is taken without anticoagulant and is immediately centrifuged with moderate forces during 12 minutes. Three layers appear then in the tubes: the red blood cells are gathered at the bottom, acellular plasma is at the top of the

tube and a strongly polymerized fibrin clot called PRF is formed between [36]. This PRF clot gathers most of the platelets and half of the leukocytes (mostly the lymphocytes) of the blood sample [36], and it was therefore called Leukocyte- and Platelet-Rich Fibrin (L-PRF)[1]. It can be used clinically as a clot or as a membrane [37]. In comparison with PRP gels, this PRF gel is particularly strong, and releases significantly during more than 7 days large quantities of key coagulation and healing molecules (thrombospondin-1, fibronectin, vitronectin) and growth factors - particularly the platelet growth factors TGF β 1 (Transforming Growth Factors β 1), PDGF (Platelet-Derived Growth Factors) and VEGF (Vascular Endothelial Growth Factor)[38,39].

This clot is produced without blood modification, and can be considered as an optimized natural blood clot, prepared in a clinically usable form [36]. It is a solid biomaterial and not a liquid suspension: therefore it can not be injected like the various PRPs [6] and it only exists in an activated gel form. Reported in vitro and in vivo experimental effects were very positive and significant [40-42]. This family of platelet concentrates developed nowadays very strongly with excellent results in periodontology [43-45], oral surgery [46] and implant dentistry [47-51]. This strong fibrin membrane/clot form is particularly adapted to oral clinical applications [24,25], even if other applications in orthopedic and sports medicine [52] and for the treatment of chronic skin ulcers are also advocated [53].

After several years of experimental use by clinicians at the borderline of the local regulations [54], the production system and kit are now marketed and available as a CE-marked and FDA-approved inexpensive system called Intra-Spin (Intra-Lock, Boca Raton, Florida, USA), as shown in the **Figure**.



Figure. The centrifuge and kit for the preparation of Intra-Spin L-PRF (Intra-Lock, Boca Raton, FL, USA). This system is the CE-marked FDA-approved version of the well-known open-access technique for the production of L-PRF clots and membranes. All the systems for the production of platelet concentrates on the market require a specific centrifuge (the model on the photo is one of the most compact) and an adapted collection and preparation kit (in this case, mostly tubes and a box of collection). The ergonomics of the final system is an important parameter for the development of these techniques in daily use.

2.4. Evolutions of the terminology

While the literature about PRPs developed with all these contradictions, several authors started to point out the need for a more accurate terminology and the importance of some neglected parameters, such as the leukocyte contents and the fibrin architecture.

In an opinion published in 2006, Bielecki et al. [55] insisted on the different forms of PRP used in clinical practice: PRP can be injected without activator (for example in injured tendons or articulations)[6], but is more often used after activation resulting in a gel formation. It was therefore proposed to call Platelet-Rich Plasma the suspension, and “Platelet-Rich Gel” (PRG) the activated fibrin gel. The 2 forms are not the same products. The authors also pointed out the presence of leukocytes in these preparations, and the need to take them into consideration. In 2008, Everts et al. [56] insisted on the importance of the leukocytes and the activation in the biology of the PRPs. These authors suggested to name the inactivated suspension “platelet-leukocyte rich plasma (P-LRP)”, and the activated gel “platelet-leukocyte gel (PLG)”. These two terminologies were used in a few articles [57-60].

However, these suggested terminologies remained incomplete, as not all PRPs have leukocytes [61], and PRPs do not require to be activated prior to injection to be active (they activate in a different way after injection in the host tissue)[6]. Moreover, after activation of a PRP, the gels never reach the strength of natural fibrin polymerization obtained in the PRF subfamily [36,62]. The definition of a more global terminology for all platelet concentrates was needed, in order to integrate all the potential configurations and components of these preparations. A classification system was finally published [1] and confirmed through a first international consensus article [11]. This system will serve as a basis of the POSEIDO recommendations.

3. Current POSEIDO terminology

3.1. Classification system

The POSEIDO recommendations are based on the previously published classification of platelet concentrates for surgical use [1], and will serve as a basis for future evolutions of the terminology and recommendations for clinical use.

First, all the products of this category are regrouped under the general term of “platelet concentrates”, whatever their form or cell content.

Second, it is important to highlight the key influence of the leukocyte content [63-65] and fibrin architecture [66,67] in the potential clinical or experimental effects of these products, and that each product refers to a specific biological imprint [39,68,69].

Four families can be highlighted, based on their leukocyte and fibrin content. Liquid platelet concentrate suspensions (before activation) are termed Platelet-Rich Plasma (PRP): “Pure Platelet-Rich Plasma” (P-PRP) without leukocytes, “Leukocyte- and Platelet-Rich Plasma” (L-PRP) with leukocytes. On the other side, solid platelet concentrate biomaterials, with a strong fibrin architecture (therefore existing only in this activated form), are termed Platelet-Rich Fibrin (PRF): “Pure Platelet-Rich Fibrin” (P-PRF) without leukocytes, “Leukocyte- and Platelet-Rich Fibrin” (L-PRF) with leukocytes. The activated versions of a P-PRP and a L-PRP are respectively a « P-PRP gel » and a « L-PRP gel ». The 2 PRF subfamilies only exist in the gel form, per definition. The main described technologies are classified in the **Table**.

This basic terminology has the advantage to be simple and to avoid commercial interference [70]. It may not be enough to avoid the many possible experimental bias detected in the literature [45,71-73], but it is a first important step to create a minimal common basis for terminology and characterization of marketed or experimental products.

Platelet Concentrate Class and terminology	Methods of production (generic name, detailed appellation when existing, company, city, country)[references]
P-PRP (Pure Platelet-Rich Plasma) , before activation (P-PRP gel , after activation)	AP - Cell separator PRP (experimental)[7] - Vivostat PRF (Vivolution, Allerød, Denmark)[31]
	MP - PRGF/Endoret (Preparation or Plasma Rich in Growth Factors, BTI BioTechnology Institute, Vitoria, Spain)[61,70] - E-PRP (Eye Platelet-rich Plasma, experimental)[8] - Nahita PRP (Nahita, Navarra, Spain)[28]
L-PRP (Leukocyte- and Platelet-Rich Plasma) , before activation (L-PRP gel , after activation)	AP - PCCS PRP (Platelet Concentrate Collection System, 3I, Palm Beach Gardens, FL, USA)[26,31] - SmartPreP PRP (Harvest Corp, Plymouth, MA, USA)[27,31] - Magellan PRP (Magellan APS (Autologous Platelet Separator), Medtronic, Minneapolis, MN, USA)[30] - Angel PRP (Angel Whole Blood Processing System (AWBPS), Sorin Group, Mirandola, Italy) - GPS PRP (Gravitational Platelet Separation System, Biomet Biologic, Warsaw, IN, USA)[69]
	MP - Friadent PRP (Friadent-Schütze, Vienna, Austria)[27] - Curasan PRP (Curasan, Kleinostheim, Germany)[26] - Regen PRP (Regen Laboratory, Mollens, Switzerland)[32] - Plateltex PRP (Plateltex, Prague, Czech Republic)[29] - Ace PRP (Surgical Supply and Surgical Science Systems, Brockton, MA, USA)[28]
P-PRF (Pure Platelet-Rich Fibrin)	MP Fibrinet PRFM (Cascade Medical, Wayne, NJ, USA)[31,32]
L-PRF (Leukocyte- and Platelet-Rich Fibrin)	MP - Intra-Spin L-PRF (Intra-Lock, Boca Raton, FL, USA)[36,37] - Titanium-prepared PRF (experimental)[42]

Table. Classification of the main available methods of production of platelet concentrates, in the 4 main families of products. In each category, many marketed or experimental custom-made protocols exist. Even if all techniques use similar concepts and fall within the limits of this classification system, the possible variations of production techniques are endless and this table regroups only some significant well-defined products. Some techniques require little handling and are considered as Automated Procedures (AP), while others require more handling steps and are considered as Manual Procedures (MP).

3.2. Potential evolutions of the classification

At this point of our knowledge, three last parameters are still kept outside of this classification system: the platelet concentration rate, the leukocyte concentration rate, and the proportion of the various sorts of leukocytes. Indeed, even if these parameters may have

some impact, their exact clinical influence remains still too vague, particularly in oral and maxillofacial applications.

Platelet concentrations can be very different between the various systems [35,61,74] but the immediate effects of dilution undermine the impact of this parameter in vivo. Mishra et al. [75] suggested a specialized sub-classification for injectable PRPs in sports medicine, where a 5-fold platelet concentration rate may be a relevant baseline for the definition of PRP subfamilies (concentrations higher than 5-fold often gave better clinical results). However, this baseline is probably not universal and therefore not valid for all clinical applications. This issue does not exist in the PRF family, where all the platelets of the blood sample are activated and integrated in the fibrin matrix of the clot [36].

The leukocyte concentration and formula may also have an impact [63,68], but they were often neglected in the literature. Their influence should be investigated carefully in the future, as their presence or not may explain many contradictory results that were observed, particularly in sports medicine and orthopedic surgery [75].

There is a very last parameter that remains even more unclear than the others: the global cell content of the L-PRP and L-PRF [3]. Indeed, the products containing leukocytes in fact also contains a large and diverse population of circulating cells, all of them interacting and influencing their environment [40]. The control and adequate management of these cells may open new therapeutic opportunities.

All these parameters should be assessed carefully now, in order to develop with accuracy our knowledge and maybe improve this first classification system in the future.

4. Perspectives

It is important to notice the current evolution of the use of platelet concentrates in the interconnected fields of periodontology, oral surgery, esthetic and implant dentistry (POSEID disciplines). Even if they are used with some success for the treatments of chronic skin ulcers and in sports medicine, PRPs are slowly disappearing from the POSEID fields, due to their complexity of use, costs of production, and mixed clinical results. On the other hand, the development of the L-PRF in the POSEID fields is accelerating, as it can be observed in the number of publications appearing recently. The reasons are very simple and pragmatic: the L-PRF is inexpensive, easy to use and efficient in many oral applications. In short, the technology meets the criteria of daily use of the specialists. This is now an important topic of research in the POSEID disciplines.

As a conclusion, this consensus conference was designed to help both authors and readers to understand the current situation and perspectives in the field of platelet concentrates for surgical use. For authors, this classification system should be considered as guidelines for preparation of research works on this topic. This is also for our community a first step to develop research projects on this theme and improve our knowledge of these preparations. Platelet concentrates are playing and will play even more a significant role in our therapeutic strategies in the coming years, and this classification will probably be completed and improved in the future.

Disclosure of interests

The authors have no conflict of interest to report.

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