ACTA ODONTOLOGICA SCANDINAVICA, 2017
VOL. 75, NO. 1, 1–11
http://dx.doi.org/10.1080/00016357.2016.1236985

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Use of platelet concentrates in oral and maxillofacial surgery: an overview

Zornitsa Mihaylova[a], Vanyo Mitev[b], Pavel Stanimirov[a], Antonia Isaeva[b], Natalia Gateva[c] and Nikolay Ishkitiev[b]

[a]Department of Oral and Maxillofacial Surgery, Medical University Sofia, Sofia, Bulgaria; [b]Department of Medical Chemistry and Biochemistry, Medical University Sofia, Sofia, Bulgaria; [c]Department of Pediatric Dentistry, Medical University Sofia, Sofia, Bulgaria

ABSTRACT

Objective: To describe and provide a comprehensive overview on the development, use and efficacy of autologous platelet concentrates in different *in vitro* and *in vivo* studies focusing on oral and maxillofacial pathologies.

Materials and methods: Present work employs an extensive critical overview of the literature on the development and application of platelet concentrates.

Results: Platelet concentrates are innovative endogenous therapeutic agents which gained a lot of interest in different medical and dental disciplines due to their potential ability to stimulate and increase regeneration of soft and hard tissues. The effect of platelet-derived products is considered to be a result of the high number of platelets which contain a wide range of growth factors. They are not just therapeutic products but autologous blood concentrates containing active molecules. The quality of platelet concentrates may vary according to the individual physical state of donors making it difficult to to compare the outcomes of their application. Although, there are many studies analyzing the properties of these biomaterials both *in vivo* and *in vitro*, a consensus regarding their efficacy still has to be reached.

Conclusion: Evidences described in the literature on the efficacy of platelet concentrates in procedures in oral and maxillofacial region are controversial and limited. In order to clarify the real advantages and priorities for the patients, when the blood-derived products are applied, further *in vitro* and *in vivo* research about the activity of PRP and PRF on the dental cells biology should be conducted.

ARTICLE HISTORY
Received 12 March 2016
Revised 4 August 2016
Accepted 9 September 2016
Published online 27 September 2016

KEYWORDS
Platelet-rich fibrin; platelet-rich plasma; tissue regeneration

Introduction

The success of complete self-regeneration in many tissues and organs after injury is limited. In endogenous regenerative medicine, tissue recovery is stimulated by blood plasma, growth factors and cytokines from platelets.[1,2]

Many studies focused on the development of innovative methods for tissue regeneration based on the use of different graft materials (auto-, allo- and xenografts), growth factors, cytokines, scaffolds or a combination of them.[3–5] An interesting group of biomaterials for local applications are the blood-derived products. Several types of biomaterials can be purified from human blood. They are usually divided into products with high amount of fibrinogen and products with high amount of platelets.[4]

Platelets and especially the growth factors they contain in combination with plasma proteins are expected to participate in tissue regeneration, healing process and blood clot formation. The primary intention for the application of platelet concentrates in clinics is activation of proliferation, migration and differentiation of the available cell reserve in the wound area ultimately leading to a successful regenerative process. This is of high importance, especially when the number of cells in the place of tissue injury is reduced.[5] Biomaterials used recently in clinics, whose effect is based on the platelets' function are Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF). Their applications include the field of oral and maxillofacial surgery, plastic surgery, orthopedic surgery, etc.,[6,7] but with controversial results.

The aim of this review is to critically estimate the methods of deriving the biomaterials, to analyze their *in vitro* effectiveness and to underline future research topics for better and more consistent clinical results.

Structural components of tissue regeneration

Scaffolds and stem cells

Large soft and hard tissue defects in the oral and maxillofacial region can be observed due to infections, trauma, tumors, congenital issues, etc. Some of the most widely investigated strategies for the reconstruction of these deformities are the application of autologous bone grafts and soft tissue flaps. However, the use of these materials could lead to complications even though they are autologous.[8] Therefore, the main goal for tissue engineering is to keep developing innovative methods for the maintenance and improvement of tissue rehabilitation, integrity and function.

CONTACT Nikolay Ishkitiev ishkitiev@fdm.mu-sofia.bg, ishkitiev@gmail.com Department of Medical Chemistry and Biochemistry, Medical University Sofia, Zdrave 2 str., 343, Sofia 1433, Bulgaria

Tissue regeneration consists of precisely regulated interactions between the three basic components: cells, growth factors and scaffolds or extracellular matrix (ECM).[9] A wide range of biocompatible, biodegradable and nontoxic synthetic or natural biomaterials are used as careers or scaffolds in tissue regeneration, to provide local mechanical strength and to facilitate the process of attachment, proliferation and differentiation of stem and progenitor cells.[10] In the natural scaffolds group are included collagen, elastin, fibrin, silk, chitosan, glycosaminoglycan, and alginate.[11] Widely used synthetic polymer scaffolds in regenerative medicine are poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(-ethylene glycol) (PEG), polycarbonates, polycaprolactones, polyorthoesters, etc.[12–15] Polymer hydrogels which have been recently introduced as scaffold biomaterials possess excellent biocompatibility and soft tissue-like mechanical features.[13] Platelet concentrates are also a promising tool as grafting materials in the field of regenerative medicine due to the high amount of active molecules they supply locally and the dense fibrin network formed, able to be colonized by various cell types.

The development of regenerative therapy has significantly been influenced by the progress of stem cell research. They represent a population of undifferentiated cells, mainly characterized by the ability of self-renew and multi-lineage differentiation.[14] Three different types of stem cells have been described: embryonic stem cells (ES), adult or somatic stem cells and induced pluripotent stem cells (iPS).[15] ES are pluripotent cells delivered from the blastocyst, capable of differentiation to cell types of the three germinal layers but not to extraembryonic cell lineages.[16] iPS are delivered by genetic manipulations of somatic cells being also considered pluripotent.[17] There are major ethical and technical restrictions concerning the research and application of ES and iPS.[18]

Mesenchymal stem cells (MSC) can be found in various mesenchymal organs throughout the lifespan, where they support tissue homeostasis.[15] These cells are multipotent because their differentiation potency is more limited in comparison with ES and iPS. MSC are expected to undergo differentiation mainly into cell types identical to their tissue of origin,[19] however there are a wide range of studies investigating their ability of multilineage differentiation. The International Society for Cellular Therapy (ISCT) defined the following minimum criteria for MSC: 1. Plastic adherence in standard culture conditions; 2. Multilineage differentiation to osteoblasts, adipocytes, chondrocytes; 3. Expression of CD73, CD90, CD105, and lack of expression of CD11b, CD14, CD19, CD34, CD45, CD79α, HLA-DR.[20] MSC have been isolated from various tissues like bone marrow,[21] placenta,[22] adipose tissue,[23] etc. A new era in regenerative medicine and dentistry arises with the affirmation of stem cells as promising candidates for tissue regeneration and repair.

Bone marrow MSC are some of the most investigated types of stem cells. The main disadvantage here remains the local trauma and morbidity at the site of delivery and the general anesthesia required for their isolation. An attractive alternative source of MSC is the dental tissue. Several types of MSC with dental origin have been described [24] – dental pulp stem cells (DPSC), stem cells from exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSC), stem cells from apical papilla (SCAP), dental follicle progenitor cells. These stem cells possess all the properties needed to be classified as MSC, including self-renewal and multilineage differentiation ability.[19] They are capable in an appropriate environment to differentiate into a wide range of cell types-osteoblasts, chondroblasts, adipocytes, pancreatic-like cells,[25] hepatocyte-like cells,[26] etc. The identification of MSC from dental tissues increases the clinical interest in MSC as an appropriate source for regeneration of several connective tissue structures such as cementum, dentin and periodontal ligament (PDL).[27] Many scientific groups have used MSC with dental origin to clarify their biological properties and possible clinical applications. DPSC have demonstrated the ability to generate dentin/pulp-like complexes when applied with hydroxyapatite/tricalcium phosphate.[28] It is been shown that hydrogel scaffolds obtained from bone ECM upregulates the odontogenic differentiation and odontogenic markers expression in DPSC culture *in vitro* without the addition of any growth factors and inducers.[29] Other experimental studies reveal the potency of PDLSC to regenerate periodontal tissue.[30] These cells are capable in appropriate conditions to regenerate cementum/periodontal ligament-like structures and are also suggested to contribute to alveolar bone regeneration.[31] SHED have been found to promote wound healing.[32] It has been demonstrated that oral stem cells are able to repair the following tissues: cornea, dental pulp, periodontal, neural, bone, muscle, tendon, cartilage, and endothelial tissues without neoplasm formation.[33] Some of the disadvantages about dental MSC research are probably related to the fact that the isolated cell culture is heterogeneous with relatively low stem cells percent, which requires further cultivation and expansion in suitable conditions. At the same time, not all adults should undergo third molar extraction. To resolve these drawbacks, scientists keep looking forward for investigating newer approaches for stem cell-based therapy. Thus, MSC derived from periapical cyst have been found to differentiate to osteogenic and adipogenic cell lineages.[34]

Platelets and growth factors

Platelets are delivered by megakaryocytes in bone marrow. Their size is approximately 2–3 μm in diameter. The main function of platelets is known to be prevention of excessive bleeding and repair the blood vessels' wall after injury.[35] Platelets become activated as a result of their contact with collagen revealed after damaging the vascular endothelium. Platelets are responsible for the first phase of blood clotting. It includes adhesion, activation and aggregation of the platelets. Activated platelets change their shape and release granules in the extracellular space. Other platelets are also getting involved in the clot formation at the site of tissue injury by the process of co-activation and stimulation of chemotaxis.

Platelets participate not only in hemostasis but also in angiogenesis, inflammation, antibacterial safety, tissue

regeneration.[36] Although their main role is blood clot formation, they also contain growth factors, enzymes and other proteins. They have plenty of alpha-granules, which are the main reservoir of growth factors.[37]

The size of alpha-granules is about 500 nm and their number in one cell is approximately 50–80. They are known to have heterogeneous contents.[38] Some of their molecules have opposing effects. Alfa-granules are released through exocytosis once the platelets are activated.

Growth factors from platelets' alpha-granules are small polypeptides with molecular weight of about 6–45 kDa. They have chemotactic and mitogenic properties, modulate cell functions and proliferation, stimulate regeneration of soft and hard tissues after damage.[39–41] Growth factors bind to specific receptors on the target cells' surface and initiate protein synthesis, collagen and osteoid-like tissue accumulation.[42] Some of the most important growth factors are platelet-derived growth factors (PDGFs), transforming growth factor-beta (TGF-beta), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), etc.[37,43] Usually they have multi-functional effects and the result of their action depends on their proportion and the distribution of growth factors' receptors on cell surface. Platelet concentrates improve conditions for tissue regeneration by providing increased local level of growth factors and their therapeutic properties. Many preclinical and clinical studies have been performed to demonstrate the benefits of the growth factors use.[44]

The knowledge on platelets' function and all the active molecules they contain, represent a strong base for the development and introduction in the medical fields of this fairly new type of biomaterials known as platelet concentrates. They could be described as products which arise from the fibrin glues but are enriched with platelets.

Development of the blood-derived products: from fibrin adhesives to platelet concentrates

Fibrin adhesives

The use of products delivered from human blood for wound sealing and stimulation of healing processes started more than 40 years ago. The idea for platelet concentrates application in surgical fields actually arises from another product called fibrin adhesive or sealant. It is well known that the fibrin matrix is an end product of the coagulation cascade. The adhesive properties of fibrin have been revealed by Bergel in 1909. Fibrin glue is the first biomaterial composited by concentrated fibrinogen.[45] Thrombin and calcium are also necessary here to initiate the polymerization process. The application of fibrin (from concentrated fibrinogen and factor XIII) on regeneration of human nerve fibers is demonstrated by Matras in 1972.[46]

Fibrin is naturally able to support the process of hemostasis. After surgical intervention, a tight adhesion would be achieved between the applied fibrin biomaterial and the wound surface. Thus, a bleeding control is accomplished and also the healing process is optimized.[47]

Fibrin glue is represented as two-component system. The first component contains fibrinogen and factor XIII. The second one contains human thrombin, calcium and antifibrinolytic agent. The main active proteins in fibrin adhesives are concentrated fibrinogen and thrombin. After mixing fibrinogen and thrombin, a three-dimensional network is obtained that can be colonized by different cell types. These two agents are mixed right before their local application. It takes several seconds for the required texture to be achieved and the material adheres to the tissues. The whole process resembles the last step of coagulation cascade called thrombin-induced conversion of fibrinogen to fibrin.[48] Mechanical properties of the fibrin matrix depend on the fibrinogen concentration, the polymerization speed depends on the thrombin concentration.[49,50] Fibrin adhesives generally do not contain any platelets or growth factors and cytokines. After a period of about 2 weeks they are completely resorbed by macrophages and fibroblasts.[51]

Fibrin biomaterials can be divided by their delivery route. They are delivered by large plasma pools, volunteers in hospitals with blood banks or point-of-care centers. The fibrin adhesive by Matras (Tisseel, Immuno, Vienna, Austria) is associated with risk of viral transmission because of its origin. Thus, fibrin glues could also be allogeneic or autologous.[52,53] When the application of autologous fibrin glues is performed, the risk of contamination is decreased because the biomaterial is delivered by patients' own blood. Nevertheless, the problem with the intricate delivery protocol still persists.[54]

Fibrin adhesives find application for prophylaxis of postoperative hematomas, prevention of excessive bleeding, especially on patients with coagulation disorders (an exception is bleeding from wide lumen vessels), decreasing tension after flap adaptation, accelerate healing process after surgery, etc.[55]

Platelet concentrates – platelet-rich plasma (PRP)

PRP is a first generation platelet concentrate. It is obtained by fresh venous blood through centrifugation and contains high number of platelets (round about 1,000,000 platelets per μL).[56,57] There are different protocols described in the literature for PRP extraction from whole blood but all of them are based on a few general rules,[58,59] as follows: nearly 20–80 ml venous blood is drained from the patient immediately before the surgical intervention and is collected in container with anticoagulant; the anticoagulant binds calcium ions and thus prevents the prothrombin-thrombin conversion and degranulation of platelets; PRP delivery can be divided into two steps: centrifugation (soft and hard spin) and activation (Figure 1(A)). The time needed for the platelet concentrate delivery varies in protocols, but is completed usually within an hour.[59] Finally, PRP is applied at the site where it has to realize its effectiveness, together with activators (thrombin, calcium chloride). Activators cause degranulation of the platelets and polymerization of fibrin. This leads to the formation of platelet gel and release of growth factors.[38] To avoid the use of calf thrombin as PRP activator,

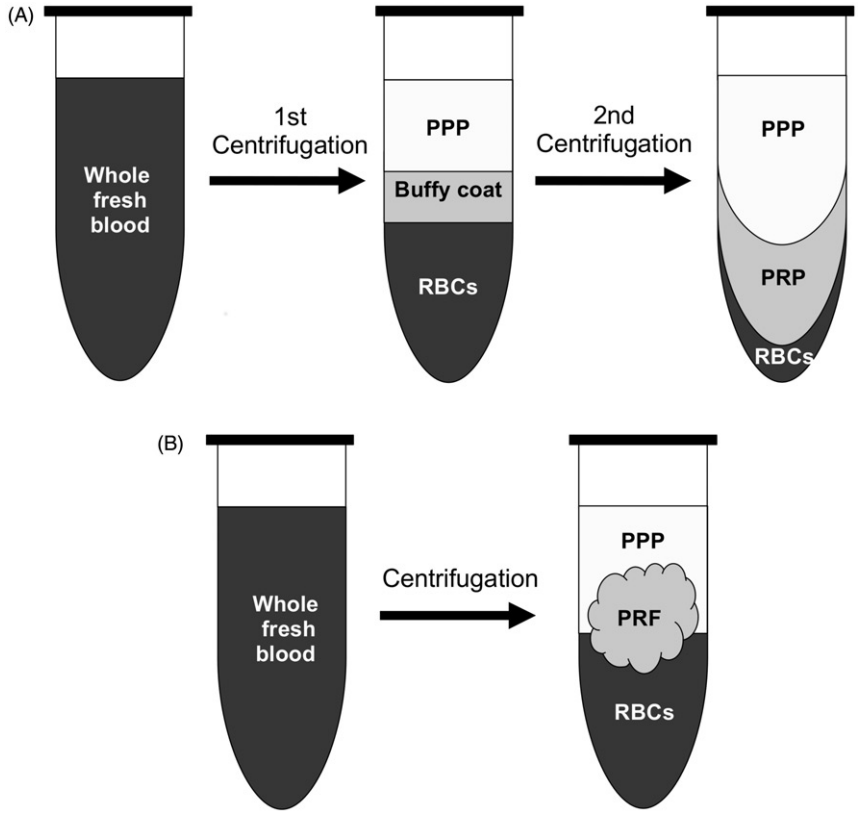

Figure 1. PRP and PRF delivery from whole fresh blood (WFB). (A) PRP delivery in two centrifugation steps. In the first centrifugation step (soft spin) the whole fresh blood is separated into three fractions: PPP, 'buffy coat' and RBCs. Only the 'buffy coat' layer is used for the second centrifugation step (hard spin) when three new fractions are delivered: PPP, PRF and RBCs. (B) PRF delivery from whole fresh blood in one centrifugation step. PRF is delivered in the middle of the tube. PPP and RBCs layers are discarded.

which is a xenofactor and can lead to high levels of antibodies against human coagulation factors, an autologous human thrombin can be applied.[60] As an alternative for the activation of PRP, type I collagen can be used, which leads to slower degranulation of platelets and growth factors release.[61] Thrombin, calcium chloride and collagen are effective enough when used to activate both platelets and fibrinogen.

The release of growth factors starts within the first 10 minutes when the platelet concentrate is ready for use and nearly 95% of them get secreted within the first one hour after activation of platelets.[62,63] That means PRP has to be applied in the tissues within the first 10 minutes after activation. If not activated PRP could stay stable with vital platelets for round about 8 hours.[62] PRP delivery requires collecting of a small amount of blood, and thus an infusion or re-infusion of blood or blood products is not necessary to be carried out.[64] There is no risk for the patient of abnormally low levels of hemoglobin, hematocrit and platelet number.[65]

In humans the number of platelets varies individually between 150,000 and 450,000 per μL blood. Depending on the protocol used for the PRP preparation, the platelet number in platelet concentrate could vary. It could be 2–5 times or more above the physiological level. If the platelet concentrate has lower amount of platelets, a suboptimal effect may be observed as the higher number platelets can inhibit the processes.[66] It is important that the amount of growth factors depends on the number of platelets in the whole fresh blood drawn for the preparation of PRP.[67] Patient's gender influences the properties of the blood product, whereas the age does not.[57]

As an autologous biomaterial, PRP possesses properties like lack of toxicity and immunogenicity.[62,68] Platelets also secrete locally signal molecules which are attractants for macrophages.[69] It is expected to participate in the nonspecific immunity due to the small number of white blood cells able to synthesize interleukins.[70] Although recent evidence suggests that pure PRP possesses antimicrobial properties, it makes the presence of leukocytes for this purpose unnecessary.[71]

For some patients with bleeding disorders, conditions like coagulopathies and anticoagulation therapy drawing blood might be contraindicated. In these cases probably an allogeneic PRP application could be a better choice to avoid complications, related to the patients' general status.[72] Whereas, Marx [64] in his study avers that the use of allogeneic blood for PRP delivery leads to false-negative results. According to his opinion, the real PRP should always be autologous.

Platelet concentrates – platelet-rich fibrin (PRF)

PRF is a second generation platelet concentrate.[73,74] This product is introduced in France in 2001 considering the restrictions about replantation of biochemically processed

Table 1. Dohan Ehrenfests' platelet concentrates classification-four categories of platelet concentrates and their delivery protocols are listed.

Platelet concentrate:	Protocols
Leukocyte – poor or pure platelet-rich plasma (P-PRP)	– Plasmapheresis – Vivostat PRF – Anitua's PRGF
Leukocyte- and platelet-rich plasma (L-PRP)	Manual protocols for L-PRP: – Curasan PRP kit (Curasan Pharma Gmbh AG, Lindingstrab, Kleinostheim, Germany) – Regen PRP (Regen Laboratory, Mollens, Switzerland) – Friadent-Schutze (Vienna, Austria) – Plateltex (Bratislava, Slovakia) Automated protocols for L-PRP: – Smart PreP Autologous Platelet Concentrate System (Harvest Technologies Corp, Plymuth, MA) – Platelet Concentration Collection System – PCCS (3I Implant Innovations, Palm Beach Gardens, FLA) – Magellan Autologous separator (Medtronic Inc, Minneapolis, MN) – GPS (Gravitational Platelet Separation System, Biomet Biologic, Warsaw, USA)
Leukocyte – poor or pure platelet-rich fibrin (P-PRF)	Fibrinet PRFM kit (FIBRINET, Cascade Medical Enterprises, Wayne, NJ, USA)
Leukocyte and platelet-rich fibrin (L-PRF)	Choukroun's PRF

blood products. It is described as platelets and leukocytes-rich fibrin biomaterial.[75,76] PRF is delivered in silica gel-coated plastic tubes without any addition of anticoagulants and other substances, like bovine thrombin, calcium chloride or other activators, using a simple method.[75]

Briefly 10–80 ml autologous venous blood is distributed in 10 ml dry sterile silica gel-coated plastic tubes without the addition of anticoagulant and is centrifuged at 2700 or 3000 rpm (about 400g) for 10–12 minutes. Three layers are established: PPP (platelet-poor plasma) above, red blood cells (RBC) at the bottom and PRF in the middle. The middline layer is where exactly the platelets and white blood cells are concentrated.[73,75,76] Platelet activation and fibrin polymerization are accomplished in natural way. Platelets are activated as a result of contact with the wall of the tube. Dense fibrin network as a result of activation could entrap growth factors for longer and protect them from proteolysis [77] (Figure 1(B)).

Centrifugation has to be performed immediately when the blood is drawn (within 2 min 30 s). If not, a diffuse fibrin polymerization begins in the whole glass tube and platelet concentrate cannot be established. PRF has to be taken out of the container right after the end of centrifugation to avoid its precipitation at the bottom and mixing with erythrocytes.

Studies on PRF reveal that together with the high amount of growth factors released with the activation of platelets, there are also immune cytokines included like interleukin (IL) 1-beta, IL-6, IL-4, tumor necrosis factor (TNF).[76] This is a presumption for its local application in case of an inflammation.

Dense fibrin membranes can be obtained from PRF after pressing the biomaterial between sterile gauzes. This membrane is considered to be able to release growth factors (like TGFb-1, PDGF, VEGF) and matrix proteins (thrombospondin, fibronectin, vitronectin) during several days.[78] Different studies reveal possibilities about the application of PRF membrane for interventions in oral and maxillofacial surgery,[73,79,80] plastic surgery,[81] otorhinolaryngology,[82] etc. According to investigations by Burnouf et al. [83] and Su et al.,[84] the amount of released growth factors decreases when PRF membrane is obtained through compression with gauze because of the high number of damaged platelets. A device called PRF-compressor has been proposed for obtaining PRF membrane, by which platelets keep their integrity.[60] It has two spoon-like surfaces. Between them PRF is pressed and 1 mm thick membrane is established.

Classification of platelet concentrates

The efficiency of platelet concentrates' topical application is still controversial. From their initial introduction in preclinical and clinical studies, a wide range of delivery protocols has been used. However, their application is confusing because each method leads to a different product with different biology and potential uses. Thus, all the results of their use in experiments are hard to compare. A classification of the platelet concentrates has been presented by Dohan Ehrenfest et al. [59] (Table 1).

Biomaterials are classified into four categories, depending on their leukocyte and fibrin content and by three main sets of parameters:

- the preparation kits and centrifuges used
- the content of the concentrate
- the fibrin network that supports the platelet and leukocyte concentrate during it's application

In vitro *application of the platelet concentrates*

Although the application of PRP and PRF in the oral and maxillofacial surgery has been established by various clinical studies, their mechanisms of action on cellular level remain poorly understood. It is well known that these products contain a wide range of active molecules acting together in biological processes. The *in vitro* studies revealing the effects of platelet concentrates especially on cells with dental origin are still very scarce. We have not found any exhaustive studies focusing the effects of platelet concentrates over the stem cell properties of cell cultures with dental origin. Caceres et al. [85] investigated the potency of thrombin-activated PRP to stimulate the adhesion, migration and myofibroblastic differentiation of human gingival fibroblasts.

Another study showed the effect of various concentrations PRP (100, 50, 20 and 10%) and PPP on proliferation and calcium nodules formation of osteoblasts and periodontal ligament cells.[86] At 24h DNA synthesis was suppressed, but over a 5-day period a beneficial outcome has been observed. PPP and 50% PRP showed the greatest enhancement of cell proliferation and differentiation. Furthermore, Lee et al. [87] assessed the efficacy of PRP on human dental stem cells obtained from periodontal ligament and dental pulp. Their analysis revealed that the colony-forming ability and cellular proliferation of dental cells were increased at 0.5 and 1% PRP but decreased at 5% concentration. PRP also promoted calcium deposits formation of both cell types after treatment with 1% concentration of the platelet concentrate.

Some of the studies describing the effects of PRP on cell cultures show lack of beneficial outcomes. Cenni et al. [88] found no statistical differences in fibroblasts and osteoblasts proliferation and functions between serum-free media and platelet gel cultivation.

We also found a very low number of experiments investigating the PRF effects over cell cultures with dental origin. A study conducted by Tsai et al. [89] showed that PRF modulates cell proliferation in a cell type-specific manner. They concluded that PRF is capable to stimulate proliferation of osteoblasts, periodontal ligament cells and gingival fibroblasts during a 3-day culture period, but suppressed oral epithelial cell growth. Another *in vitro* experiment evaluated the influence of PRF membrane over the proliferation, osteoprotegerin expression and alkaline phosphatase activity of dental pulp cells.[90] PRF did not interfere with cell viability but increased significantly cell proliferation and markers expression. Increased expression of same markers (osteoprotegerin and alkaline phosphatase activity) has been observed in human periodontal ligament cells after cultivation with PRF membrane.[91]

To the best of our knowledge, there is a limited number of *in vitro* experiments which demonstrate the influence of the platelet concentrates on cells with dental, oral and maxillofacial origin. There are certain experimental studies described, but they cannot serve as a proper base for predictability of the clinical studies results.

Platelet concentrates in clinical studies

Due to the comparatively easy application of PRP and PRF in clinical cases there is wide range of studies investigating their value for local tissue regeneration. In dental medicine PRP is usually applied with the intention of enhancing tissue regeneration in periodontal defects, alveolar socket after tooth extraction, osseointegration around dental implants, guided tissue regeneration, etc.[92–94] For first time PRP has been used in a clinical experiment by Marx et al.[62] The study included 88 mandibular bone defects. Some of them were treated with autologous bone and some with autologous bone in combination with PRP, thus demonstrating that PRP significantly increases bone regeneration. Since then many clinical studies have been conducted to reveal the effects of PRP on tissue regeneration in the oral and maxillofacial region, but most of them are hard to compare and systematize.

Tooth extraction is the most common oral surgical procedure. It could be very simple manipulation, but serious complications may occur in some cases like pain, swelling, trismus, inflammation, etc. Many studies have been conducted in the past few years to assess the efficacy of PRP application in post-extractional alveolar sockets. Covering the extraction wound with platelet concentrate is expected to prevent adverse reactions occurrence like dry socket and abscess formation. Various results showed significant improvement in the local conditions after PRP has been applied.[95–99] These studies reveal that the high amount of growth factors released in the alveolar socket after tooth extraction increases tissue regeneration and prevents local complications occurrence. Although, there are some investigations with contradictory outcomes.[100,101] They show no significant effect of PRP applied for bone regeneration after tooth extraction.

PRP could be applied on dental implant surface to increase the process of osseointegration and new bone formation after the implant placement. Some studies show significantly favorable outcomes.[102,103] However, Casati et al. concluded that PRP alone do not enhance bone regeneration in peri-implant defects.[104]

Particularly, controversial remains PRP application in periodontal surgery. Many studies reveal increased tissue regeneration when PRP is used in combination with other grafting materials,[105–107] while other experiments show no improvement after the placement of the platelet concentrate at all.[108–110]

PRP has been investigated in relation to bone regeneration in sinus floor augmentation procedures applied with β-tricalciumphosphate grafting material.[111] Results demonstrate that the combination of PRP and β-tricalciumphosphate slightly increases new bone formation (with only 8–10%) in comparison with β-tricalciumphosphate used alone and PRP does not lead to ceramic bone substitutes faster degradation. Other studies also reveal the positive effect of PRP applied together with grafting material for sinus floor augmentation.[112,113] However, Cabbar et al. [114] established that the combination of xenograft and PRP had no beneficial effect for bone formation after maxillary sinus augmentation prior to dental implants placement.

A wide range of studies [115–118] determined successful outcomes after PRP application in the treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Studies report that the use of surgical debridement procedures together with autologous PRP markedly promotes bone and soft tissue regeneration, neovascularization and decreases tissue inflammation.

Most of the studies which demonstrate positive effects after PRP use, especially over the bone formation, do not express significantly strong results. According to some opinions PRP has a rather low regenerative capacity and may influence the early phase of bone healing with short time effect which is flattening between 3rd and 6th months of application.[119] Considering reviews published recently many of the clinical cases with application of PRP described

in the literature, do not represent a statistically significant base for convincing beneficial outcomes of treatment with PRP.[35] According to Navneet et al., many investigations do not demonstrate any significant positive effects of the platelet concentrate due to the lack of standardized protocol for PRP delivery or sometimes even due to use of PPP instead PRP.[120] They suggest the platelet number to be counted both in blood and in PRP for assurance on the properties of the platelet concentrate. The properties of the platelet concentrate could vary due to amount fresh blood, anticoagulant, centrifugation, platelet count, activation agent, amount of fibrinogen, RBC and leukocytes, etc.

PRF, a second generation platelet concentrate, is widely used in the dental surgical practice. Studies in this area also show contradictory results. PRF could be formed as a membrane capable to cover and protect the wound site and to entrap active molecules and cells.[77,78]

Recent studies demonstrate PRF potency to stimulate regeneration of soft and hard tissues after tooth extraction.[121–123] Results suggest that filling an extraction socket with PRF leads to increased healing, bone formation and could be a promising tool to facilitate alveolar ridge preparation for implant placement. Investigations conducted by Gürbüzer et al. [124] demonstrated that PRF does not enhance bone healing in mandibular third molar extraction socket.

Many findings in the scientific literature indicate that PRF represents an effective modality for human periodontal infrabony defects capable to reduce pocket depth, recessions' size and to improve clinical attachment level.[91,125–127]

PRF shows promising results also when applied to sinus augmentation therapies prior to dental implant placement. There are studies which demonstrate promising results with PRF applied as a sole grafting material for sinus-lift and implantation procedures.[128,129] Other investigations reveal that deproteinized bovine bone (Bio-Oss) when used in combination with PRF lead to significantly better outcomes for treatment of maxillary bone atrophy followed by implant placement in comparison with the use of Bio-Oss as sole tissue graft.[130,131] Despite these publications which show that PRF alone or in combination with other biomaterials significantly stimulates tissue regeneration there are also some preliminary results establishing neither an advantage nor disadvantage of the application of PRF in combination with deproteinized bovine bone mineral in sinus augmentation after 6 months period.[132]

Although, many authors claim PRF has remarkably beneficial effects for tissue regeneration over PRP,[133,134] further research is necessary to clarify clinical outcomes following PRP and PRFs' application in dental, oral and maxillofacial surgery.

Clinical significance and future research directions

Fibrin adhesives and platelet concentrates are blood-derived products for local application. The interest about their efficiency in different disciplines arises significantly in the past 20 years. It is widely accepted that these products stimulate regeneration in soft and hard tissues in a way that mimics the physiological healing process. This is due to the high amount of blood components like native concentration of fibrinogen, platelets and all the active molecules they contain. The content is a solid base for the commonly accepted conception for the ability of fibrin adhesives and platelet concentrates to increase and improve the healing process in soft and hard tissues.

Blood derived products are used in wide range of medical areas: orthopedic surgery, cardiology, dermatology, plastic surgery, otorhinolaryngology, recovery of non-healing wounds, etc. These biomaterials have also been proposed for various uses in the oral and maxillofacial surgery. Many studies demonstrate their potency to contribute to post-extraction alveolar socket healing, osseointegration of dental implants, sinus-lift procedures, periodontal osseous defects healing, etc. On a cellular level platelet concentrates are shown to promote cell migration and neovascularization at the side of their local application, hence together with high concentration of bioactive molecules they also serve as biomatrices for tissue regeneration.

PRP and PRF can be applied alone or in combination with different grafting materials. Some studies conclude that their efficacy in the clinic is more significant when used together with soft and hard tissue grafts in comparison with their sole application. PRP and PRF will definitely contribute to the easier managing of the grafting material, better soft tissue flap adaptation, bleeding control. Platelet concentrates are autologous which eliminates any risk of immunogenic reactions or transmissive diseases.

Vast number of studies are conducted to show the value of platelet concentrates for the tissue regeneration and repair. Their efficacy is expected due to the high amount of biologically active growth factors and cytokines they contain. In addition, when comparing the wide range of studies, it seems PRF has higher potential for regenerative therapy in clinic than PRP.

Despite the large number of empirical data from clinical studies, there is still little systematic evidence for the effect of blood-derived products over the cell processes like collagen production, extracellular matrix secretion, expression of tumor and stem cell markers, etc. Lack of constant protocols leads to lack of constant clinical results. Frequent and not always necessary application of blood derived products, especially in maxillo-facial region, leads to increase of procedures and significant increase of the cost of these procedures both for the clinicians and for patients. In order to clarify the real blood derived products' advantages for the patients, the indications for blood-derived products application and preparation protocols should be strictly generalized and systematized. Clinical advantages should be elucidated and the indications for application of blood derived products should be objectified in order to avoid their random and unnecessary application. This could be achieved with strict cooperation between the clinical and *in vitro* researchers. Further research about the activity of PRP and PRF on the dental cells biology could provide a stable basis for the clinical application of the platelet concentrates and more predictable outcomes after their use in the oral and maxillofacial region.

Disclosure statement

All authors have no potential conflict of interest.

Funding

Financial support for this study was provided by Medical University – Sofia; Grant № 42/2015 [208/14.01.2015].

References

[1] Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of sites for implants. Int J Oral Maxillofac Implants. 1999;14:529–535.
[2] Anitua E, Sánchez M, Nurden AT, et al. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol. 2006;5:227–234.
[3] Vacanti JP, Langer R, Upton J, et al. Transplantation of cells in matrices for tissue regeneration. Adv Drug Deliv Rev. 1998;33:165–182.
[4] Burnouf T, Su CY, Radosevich M, et al. Blood-derived biomaterials:fibrin sealant, platelet gel and platelet fibrin glue. ISBT Sci Ser. 2009;4:136–142.
[5] Sammartino G, Tia M, Marenzi G, et al. Use of autologous platelet-rich plasma (PRP) in periodontal defect treatment after extraction of impacted mandibular third molars. J Oral Maxillofac Surg. 2005;63:766–770.
[6] Foster TE, Puskas B, Mandelbaum R, et al. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med. 2009;37:2259–2272.
[7] Kurita J, Miyamoto M, Ishii Y, et al. Enhanced vascularization by controlled release of platelet-rich plasma impregnated in biodegradable gelatin hydrogel. Ann Thorac Surg. 2011;92:837–844.
[8] Wang KH, Inman JC, Hayden RE. Modern conceptsin mandibular reconstruction in oral and oropharyngeal cancer. Curr Opin Otolaryngol Head Neck Surg. 2011;19:119–124.
[9] Lee SJ, Park YJ, Park SN, et al. Molded porous poly (L-lactide) membranes for guided bone regeneration with enhanced effects by controlled growth factor release. J Biomed Mater Res. 2001;55:295–303.
[10] Di Silvio L, Bone tissue engineering and biomineralization. In: Boccaccini AR, Gough JE, editors. Tissue engineering using ceramics and polymers. Boca Raton (FL): CRC Press; 2007. pp. 319–334.
[11] Gomes A, Azevedo H, Malafaya P, et al. Tissue Engineering. van Blitterswijk C (Ed.). London Burlington San Diego, CA, USA: Elsevier; 2008.
[12] Martina M, Hutmacher DW. Biodegradable polymers applied in tissue engineering research: a review. Polym Int. 2007;56:145–157.
[13] Guiseppi-Elie A. Electroconductive hydrogels: synthesis, characterization and biomedical applications. Biomaterials. 2010;31:2701–2716.
[14] Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell. 2008;2:313–319.
[15] Hynes K, Menicanin D, Gronthos S, et al. Clinical utility of stem cells for periodontal regeneration. Periodontol 2000. 2012;59:203–227.
[16] Thomson JA. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145–1147.
[17] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663–676.
[18] Bongso A, Fong CY, Gauthaman K. Taking stem cells to the clinic: major challenges. J Cell Biochem. 2008;105:1352–1360.
[19] Estrela C, Alencar AHGD, Kitten GT, et al. Mesenchymal stem cells in the dental tissues: perspectives for tissue regeneration. Braz Dent J. 2011;22:91–98.
[20] Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy. 2006;8:315–317.
[21] Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet. 1970;3:393–403.
[22] Scherjon SA, Kleijburg-van der Keur C, de Groot-Swings GM, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells. 2004;22:1338–1345.
[23] Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7:211–228.
[24] Akiyama K, Chen C, Gronthos S, et al. Lineage differentiation of mesenchymal stem cells from dental pulp, apical papilla, and periodontal ligament. Methods Mol Biol. 2012;887:111–121.
[25] Ishkitiev N, Yaegaki K, Calenic B, et al. Deciduos and permanent dental pulp mesenchymal cells acquire hepatic morphological and functional features in vitro. J Endod. 2010;36:469–474.
[26] Ishkitiev N, Yaegaki K, Kozhuharova A, et al. Pancreatic differentiation of human dental pulp CD117-positive stem cells. Regener Med. 2013;8:597–612.
[27] Tatullo M, Marrelli M, Paduano F. The regenerative medicine in oral and maxillofacial surgery: the most important innovations in the clinical application of mesenchymal stem cells. Int J Med Sci. 2015;12:72–77.
[28] Gronthos S, Brahim J, Li W, et al. Stem cell properties of human dental pulp stem cells. J Dent Res. 2002;81:531–535.
[29] Paduano F, Marrelli M, White LJ, et al. Odontogenic Differentiation of human dental pulp stem cells on hydrogel scaffolds derived from decellularized bone extracellular matrix and collagen type I. PloS One. 2016;11:e0148225.
[30] Nagatomo K, Komaki M, Sekiya I, et al. Stem cell properties of human periodontal ligament cells. J Periodont Res. 2006;41:303–310.
[31] Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet. 2004;364:149–155.
[32] Nishino Y, Yamada Y, Ebisawa K, et al. Stem cells from human exfoliated deciduous teeth (SHED) enhance wound healing and the possibility of novel cell therapy. Cytotherapy. 2011;13:598–605.
[33] Xiao L, Nasu M. From regenerative dentistry to regenerative medicine: progress, challenges, and potential applications of oral stem cells. Stem Cells Cloning. 2014;7:89–99.
[34] Marrelli M, Paduano F, Tatullo M. Cells isolated from human periapical cysts express mesenchymal stem cell-like properties. Int J Biol Sci. 2013;9:1070–1078.
[35] Amable PR, Carias RB, Teixeira V, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther. 2013;4:67.
[36] Broos K, De Meyer F, Feys B, et al. Blood platelet biochemistry. Thromb Res. 2012;129:245–249.
[37] Harrison P, Cramer EM. Platelet alpha-granules. Blood Rev. 1993;7:52–62.
[38] Blair P, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. Blood Rev. 2009;23:177–189.
[39] Anitua E, Sanchez M, Orive G, et al. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 2007;28:4551–4560.
[40] Borzini P, Mazzucco L. Platelet gels and releasates. Curr Opin Hematol. 2005;12:473–479.
[41] Everts A, Knape T, Weibrich G, et al. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol. 2006;38:174–187.
[42] Schliephake H. Bone growth factors in maxillofacial skeletal reconstruction. Int J Oral Maxillofac Surg. 2002;31:469–484.
[43] Lind M. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation. Acta Orthop Scand Suppl. 1998;283:2–37.

[44] Mihaylova Z, Stanimirov P, Mitev V, et al. Platelet-derived products and periodontal ligament stem cells. Arch Stem Cell Res. 2015;2:1006.
[45] Matras H. Die Wirkungen vershiedener Fibrinpraparate auf Kontinuitat-strennungen der Rattenhaut. Osterr Z Stomatol. 1970;67:338–359.
[46] Matras H, Dinges H, Lassmann H, et al. Zur Nahtlosen interfaszikularen nerven transplantation im tierexperiment. Wein Med Wochenschr. 1972;112:517–523.
[47] Staindl O. Surgical management of rhinophyma. Acta Otolaryngol. 1981;92:137–140.
[48] Radosevich M, Goubran HA, Burnouf T. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. Vox Sang. 1997;72:133–143.
[49] Ganong W. Review of medical physiology. London: McGraw-Hill Companies; 2005.
[50] Valbonesi M. Fibrin glues of human origin. Best Pract Res Clin Haematol. 2006;19:191–203.
[51] Petersen B, Barkun A, Carpenter S, et al. Tissue adhesives and fibrin glues. Gastrointest Endosc. 2004;60:327–332.
[52] Gammon RR, Avery N, Mintz PD. Fibrin sealant: an evaluation of methods ofproduction and the role of the blood bank. J Long Term Eff Med Implants. 1998;8:103–116.
[53] Mintz PD, Mayers L, Avery N, et al. Fibrin sealant: clinical use and the development of the University of Virginia tissue adhesive center. Ann Clin Lab Sci. 2001;31:108–118.
[54] Gibble JW, Ness PM. Fibrin glue: the perfect operative sealant? Transfusion. 1990;30:741–747.
[55] Clark R. Fibrin glue for wound repair: facts and fancy. Thromb Haemost. 2003;90:1003–1006.
[56] Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent. 2001;10:225–228.
[57] Weibrich G, Kleis WK, Hafner G, et al. Growth factor levels in plateletrich plasma and correlations with donor age, sex, and platelet count. J Craniomaxillofac Surg. 2002;30:97–102.
[58] Dohan S, Dohan A, Choukroun J, et al. De l'usage des concentres plaquettaires autologues en application topique. Odontologie. 2005;1:141–180.
[59] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure plateletrich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (LPRF). Trends Biotechnol. 2009;27:158–167.
[60] Kobayashi M, Kawase T, Horimizu, et al. A proposed protocol for the standardized preparation of PRF membranes for clinical use. Biologicals. 2012;40:323–329.
[61] Fufa D, Shealy B, Jacobson M, et al. Activation of platelet-rich plasma using soluble type I collagen. J Oral Maxillofac Surg. 2008;66:684–690.
[62] Marx RE, Carlson ER, Eichstaedt R, et al. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85:638–646.
[63] Somani R, Zaidi I, Jaidka S. Platelet-rich plasma – a healing aid and perfect enhancement factor: review and case report. Int J Clinn Pediatr Dent. 2011;4:69–75.
[64] Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62:489–496.
[65] Driver VR, Hanft J, Autologel Diabetic Foot Ulcer Study Group, et al. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage. 2006;52:68–70.
[66] Weibrich G, Hansen T, Kleis W, et al. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone. 2004;34:665–671.
[67] Andrade MG, de Freitas Brandao CJ, Sa CN, et al. Evaluation of factors that can modify platelet-rich plasma properties. Oral Surg Oral Med Oral Pathol Oral Radial Endod. 2008;105:5–l2.
[68] Lynch SE. Effect of the platelet-derived growth factor/insulin-like growth factor-1 combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs. J Periodontol. 1991;62:710–716.
[69] Lindeboom JA, Mathura KR, Aartman IH, et al. Influence of the application of platelet-enriched plasma in oral mucosal wound healing. Clin Oral Implants Res. 2007;18:133–139.
[70] Wrotniak M, Bielecki T, Gazdzik TS. Current opinion about using the platelet-rich gel in orthopaedics and trauma surgery. Ortop Traumatol Rehabil. 2007;9:227–238.
[71] Mazzocca AD, McCarthy MB, Intravia J, et al. An in vitro evaluation of the anti-inflammatory effects of platelet-rich plasma, ketorolac, and methylprednisolone. Arthroscopy. 2013;29: 675–683.
[72] Smrke D, Gubina B, Damanovic D, et al. Allogeneic platelet gel with autologous cancellous bone graft for the treatment of a large bone defect. Eur Surg Res. 2007;39:170–174.
[73] Choukroun J, Diss A, Simonpieri A, et al. Platelet-rich fibrin (PRF): a second generation platelet concentrate. Part IV: clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:56–60.
[74] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: platelet related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:45–50.
[75] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate, part I: technological concept and evolution. Oral Surg Oral Med Oral Path Oral Radiol Endod. 2006;101:37–44.
[76] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:51–55.
[77] Lundquist R, Dziegiel MH, Agren MS. Bioactivity and stability of endogenous fibrogenic factors in platelet-rich fibrin. Wound Repair Regen. 2008;16:356–363.
[78] Dohan Ehrenfest DM, De Peppo GM, Doglioli P, et al. 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. 2009;27:63–69.
[79] Choukroun J, Diss A, Simonpieri A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part V: histologic evaluations of PRF effects on bone allograft maturation in sinus lift. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:299–303.
[80] Diss A, Dohan DM, Mouhyi J, et al. Osteotome sinus floor elevation using Choukroun's platelet-rich fibrin as grafting material: a 1-year prospective pilot study with microthreaded implants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:572–579.
[81] Braccini F, Dohan DM. The relevance of Choukroun's platelet rich fibrin (PRF) during facial aesthetic lipostructure (Coleman's technique): preliminary results. Rev Laryngol Otol Rhinol. 2007;128:255–260.
[82] Choukroun JI, Braccini F, Diss A, et al. Influence of platelet rich fibrin (PRF) on proliferation of human preadipocytes and tympanic keratinocytes: a new opportunity in facial lipostructure (Coleman's technique) and tympanoplasty? Rev Laryngol Otol Rhinol. 2007;128:27–32.
[83] Burnouf T, Lee CY, Luo CW, et al. Human blood derived fibrin releasates: composition and use for the culture of cell lines and human primary cells. Biologicals. 2012;40:21–30.
[84] Su CY, Kuo YP, Tseng YH, et al. In vitro release of growth factors from platelet-rich fibrin (PRF): a proposal to optimize the clinical applications of PRF. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:56–61.
[85] Caceres M, Hidalgo R, Sanz A, et al. Effect of platelet-rich plasma on cell adhesion, cell migration, and myofibroblastic differentiation in human gingival fibroblasts. J Periodontol. 2008;79: 714–720.
[86] Creeper F, Lichanska AM, Marshall RI, et al. The effect of platelet-rich plasma on osteoblast and periodontal ligament cell migration, proliferation and differentiation. J Periodont Res. 2009;44:258–265.

[87] Lee UL, Jeon SH, Park JY, et al. Effect of platelet-rich plasma on dental stem cells derived from human impacted third molars. Regen Med. 2011;6:67–79.
[88] Cenni E, Ciapetti G, Pagani S, et al. Effects of activated platelet concentrates on human primary cultures of fibroblasts and osteoblasts. J Periodontol. 2005;76:323–328.
[89] Tsai CH, Shen SY, Zhao JH, et al. Platelet-rich fibrin modulates cell proliferation of human periodontally related cells in vitro. J Dent Sci. 2009;4:130–135.
[90] Huang FM, Yang SF, Zhao JH, et al. Platelet-rich fibrin increases proliferation and differentiation of human dental pulp cells. J Endod. 2010;36:1628–1632.
[91] Chang YC, Zhao JH. Effects of platelet-rich fibrin on human periodontal ligament fibroblasts and application for periodontal infrabony defects. Aust Dent J. 2011;56:365–371.
[92] Boyapati L, Wang LH. The role of platelet-rich plasma in sinus augmentation: a critical review. Implant Dent. 2006;15:160–170.
[93] Tozum FT, Demiralp B. Platelet-rich plasma: a promising innovation in dentistry. J Can Dent Assoc. 2003;69:664.
[94] Vendramin F, Franco D, Nogueira CM, et al. Plasma rico em plaquetas e fatores de crescimento: técnica de preparo e utilização em cirurgia plástica. Rev Col Bras Cir. 2006;33:24–28.
[95] Alissa R, Esposito M, Horner K, et al. The influence of platelet-rich plasma on the healing of extraction sockets: an explorative randomised clinical trial. Eur J Oral Implantol. 2010;3:121–134.
[96] Rutkowski JL, Johnson DA, Radio NM, et al. Platelet rich plasma to facilitate wound healing following tooth extraction. J Oral Implantol. 2010;36:11–23.
[97] Ogundipe OK, Ugboko VI, Owotade FJ. Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars?. J Oral Maxillofac Surg. 2011;69: 2305–2310.
[98] Célio-Mariano R, Morais de Melo W, Carneiro-Avelino C. Comparative radiographic evaluation of alveolar bone healing associated with autologous platelet-rich plasma after impacted mandibular third molar surgery. J Oral Maxillofac Surg. 2012;70:19–24.
[99] de Marco Antonello G, do Couto RT, Giongo CC, et al. Evaluation of the effects of the use of platelet-rich plasma (PRP) on alveolar bone repair following extraction of impacted third molars: prospective study. J Craniomaxillofac Surg. 2013;41:70–75.
[100] Arenaz-Búa J, Luaces-Rey R, Sironvalle-Soliva S, et al. A comparative study of platelet-rich plasma, hydroxyapatite, demineralized bone matrix and autologous bone to promote bone regeneration after mandibular impacted third molar extraction. Med Oral Patol Oral Cir Bucal. 2010;15:483–489.
[101] Gürbüzer B, Pikdöken L, Urhan M, et al. Scintigraphic evaluation of early osteoblastic activity in extraction sockets treated with platelet-rich plasma. J Oral Maxillofac Surg. 2008;66:2454–2460.
[102] Anand U, Mehta DS. Evaluation of immediately loaded dental implants bioactivated with platelet-rich plasma placed in the mandibular posterior region: a clinico-radiographic study. J Indian Soc Periodontol. 2012;16:89–95.
[103] Anitua EA. Enhancement of osseointegration by generating a dynamic implant surface. J Oral Implantol. 2006;32:72–76.
[104] Casati ZM, Vasconcelos Gurgel CB, Goncalves FP, et al. Platelet-rich plasma does not improve bone regeneration around peri-implant bone defects-a pilot study in dogs. Int J Oral Maxillofac Surg. 2007;36:132–136.
[105] Menezes LM, Rao J. Long-term clinical evaluation of platelet-rich plasma in the treatment of human periodontal intraosseous defects: a comparative clinical trial. Quintessence Int. 2012;43:571–582.
[106] Ozdemir B, Okte E. Treatment of intrabony defects with beta-tricalciumphosphate alone and in combination with platelet-rich plasma. J Biomed Mater Res Part B Appl Biomater. 2012;100: 976–983.
[107] Saini N, Sikri P, Gupta H. Evaluation of the relative efficacy of autologous platelet-rich plasma in combination with β-tricalcium phosphate alloplast versus an alloplast alone in the treatment of human periodontal infrabony defects: a clinical and radiological study. Indian J Dent Res. 2011;22:107–115.
[108] Döri F, Kovács V, Arweiler NB, et al. Effect of platelet-rich plasma on the healing of intrabony defects treated with an anorganic bovine bone mineral: a pilot study. J Periodontol. 2009;80: 1599–1605.
[109] Keceli HG, Sengun D, Berberoğlu A, et al. Use of platelet gel with connective tissue grafts for root coverage: a randomized-controlled trial. J Clin Periodontol. 2008;35:255–262.
[110] Piemontese M, Aspriello SD, Rubini C, et al. Treatment of periodontal intrabony defects with demineralized freeze-dried bone allograft in combination with platelet-rich plasma: a comparative clinical trial. J Periodontol. 2008;79:802–810.
[111] Wiltfang J, Schlegel KA, Schultze, et al. Sinus floor augmentation with β-tricalciumphosphate (β-TCP): does platelet-rich plasma promote its osseous integration and degradation? Clin Oral Implants Res. 2003;14:213–218.
[112] Khairy NM, Shendy EE, Askar NA, et al. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation (randomized clinical trial). Int J Oral Maxillofac Surg. 2013;42: 249–255.
[113] Poeschl PW, Ziya-Ghazvini F, Schicho K, et al. Application of platelet-rich plasma for enhanced bone regeneration in grafted sinus. J Oral Maxillofac Surg. 2012;70:657–664.
[114] Cabbar F, Güler N, Kürkcü M, et al. The effect of bovine bone graft with or without platelet-rich plasma on maxillary sinus floor augmentation. J Oral Maxillofac Surg. 2011;69:2537–2547.
[115] Curi MM, Cossolin GS, Koga DH, et al. Treatment of avascular osteonecrosis of the jaw in cancer patients with a history of bisphosphonate therapy by combining bone resection and autologous platelet-rich plasma: report of 3 cases. J Oral Maxillofac Surg. 2007;65:349–355.
[116] Adornato MC, Morcos I, Rozanski J. The treatment of bisphosphonate-associated osteonecrosis of the jaws with bone resection and autologous platelet-derived growth factors. J Am Dent Assoc. 2007;138:971.
[117] Cetiner S, Sucak GT, Kahraman SA, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with zoledronic acid. J Bone Miner Metab. 2009;27:435–443.
[118] Coviello V, Peluso F, Dehkhargani SZ, et al. Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients. J Biol Regul Homeost Agents. 2012;26:151–155.
[119] Thor A, Franke-Stenport V, Johansson CB, et al. Early bone formation in human bone grafts treated with platelet-rich plasma: preliminary histomorphometric results. Int J Oral Maxillofac Surg. 2007;36:1164–1171.
[120] Navneet AS, Ramanaiake TM, Yan-Fang R, et al. Platelet rich plasma: a literature review. Implant Dent. 2009;18:303–310.
[121] Hauser F, Gaydarov N, Badoud I, et al. Clinical and histological evaluation of postextraction platelet-rich fibrin socket filling. A prospective randomized controlled study. Implant Dent. 2013;22:295–303.
[122] Peck MT, Marnewick J, Stephen L. Alveolar ridge preservation using leukocyte and platelet-rich fibrin: a report of a case. Case Rep Dent. 2011;2011:345048. doi: 10.1155/2011/345048.
[123] Zhao JH, Tsai CH, Chang YC. Clinical and histologic evaluations of healing in an extraction socket filled with platelet-rich fibrin. J Dent Sci. 2011;6:116–122.
[124] Gürbüzer B, Pikdöken L, Tunalı M, et al. Scintigraphic evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. J Oral Maxillofac Surg. 2010;68:980–989.
[125] Jankovic S, Aleksic Z, Klokkevold P, et al. Use of platelet-rich fibrin membrane following treatment of gingival recession: a randomized clinical trial. Int J Periodontics Restorative Dent. 2012;32:41–50.
[126] Lekovic V, Milinkovic I, Aleksic Z, et al. Platelet-rich fibrin and bovine porous bone mineral vs. platelet-rich fibrin in the treatment of intrabony periodontal defects. J Periodont Res. 2012;47:409–417.

[127] Sharma A, Pradeep AR. Treatment of 3-wall intrabony defects in patients with chronic periodontitis with autologous platelet-rich fibrin: a randomized controlled clinical trial. J Periodontol. 2011;82:1705.

[128] Simonpieri A, Choukroun J, Del Corso M, et al. Simultaneous sinus-lift and implantation using microthreaded implants and leukocyte-and platelet-rich fibrin as sole grafting material: a six-year experience. Implant Dent. 2011;20:2–12.

[129] Toffler M, Toscano N, Holtzclaw D. Osteotome-mediated sinus floor elevation using only platelet-rich fibrin: an early report on 110 patients. Implant Dent. 2010;19:447–456.

[130] Inchingolo F, Tatullo M, Marrelli M, et al. Trial with platelet-rich fibrin and bio-oss used as grafting materials in the treatment of the severe maxillar bone atrophy: clinical and radiological evaluations. Eur Rev Med Pharmacol Sci. 2010;14:1075–1084.

[131] Tatullo M, Marrelli M, Cassetta M, et al. Platelet rich fibrin (PRF) in reconstructive surgery of atrophied maxillary bones: clinical and histological evaluations. Int J Med Sci. 2012;9:872–880.

[132] Zhang Y, Tangl S, Huber CD, et al. 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 Craniomaxillofac Surg. 2012;40:321–328.

[133] Lauritano D, Avantaggiato A, Candotto V, et al. Is platelet rich fibrin really useful in oral and maxillofacial surgery? Lights and shadows of this new technique. Ann Oral Maxillofac Surg. 2013;1:25–29.

[134] Saluja H, Dehane V, Mahindra U. Platelet-rich fibrin: a second generation platelet concentrate and a new friend of oral and maxillofacial surgeons. Ann Maxillofac Surg. 2011;1:53.