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Platelet Rich Plasma in Periodontal Therapy

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Abstract

Technological advances in the field of medicine and allied sciences had given much needed momentum into the field of molecular biology and regenerative medicine. They indeed provided a boost to innovate new yields for both hard tissue and soft tissue regeneration in dentistry. One among them is the use of platelet concentrates - Platelet Rich Plasma [PRP], Platelet Rich Fibrin [PRF], a concentrated suspension of growth factors found in platelets which accelerates wound healing, playing a crucial role in hemostasis with well known source of cytokines and are postulated as promoters of tissue regeneration.

Numerous techniques of autologous platelet concentrates have been developed and applied in various field of dentistry. Platelet concentrates for surgical use are innovative tools of regenerative medicine, and are widely tested in the field of Periodontics. This review describes the evolution of first generation platelet concentrates Platelet rich plasma from their forerunner fibrin sealants and outlines the principles, objectives and clinical insight of its regenerative potential in periodontal therapy.

Keywords: Growth factors, Platelet concentrates, Platelet Rich Plasma, Regenerative medicine, Tissue engineering

INTRODUCTION

The goal of periodontal therapy is to improve periodontal health and thereby satisfy the functional and aesthetic needs of patients. Advances in our understanding of wound healing in the last 3 decades has shifted the goal of periodontal therapy from repair to reconstruction of periodontal tissues, thereby reversing the damage to the periodontium caused by disease process, and re-establishing the periodontal structure. Periodontal regeneration requires the complex interplay of the cells that make up the periodontium, the matrices in which they interact, and their ligands.

The use of polypeptide growth factors-platelet rich concentrate, a concentrated suspension of the growth factors in the periodontal regeneration has recently attracted the attention of periodontal researchers. Platelet concentrate contains Platelet derived growth factors, Transforming growth factors that are involved in wound healing that act as promoters of tissue regeneration. They are responsible for recruiting other cells to the site of injury, initiating vascular in-growth, and inducing cell differentiation [1]. Therefore, the term Platelet Rich Plasma is preferred to autologous platelet gel, plasma-rich growth factors (PRGFs) or a mere autologous platelet concentrate [2].The credit of introducing platelet-rich plasma into contemporary oral surgery goes to Whitman et al who first advocated its use for oral surgical procedures in 1997 [3].

This review describes the evolution of the first generation platelet concentrates - Platelet rich plasma and its application in periodontal regeneration and in other fields of dentistry.

This review article seeks to highlight the biological activities of the different Platelet concentrates and their potential applications in the field of Periodontics

Current Classification of Platelet Concentrates:

- **First generation:**
  Pure-Platelet Rich Plasma
  Leukocyte-Platelet Rich Plasma
- **Second generation:**
  Pure-Platelet Rich Fibrin
  Leukocyte-Platelet rich fibrin (L-PRF)

Platelet Rich Plasma (PRP)

The blood clot is the centre of focus of initiating all soft tissue healing and bone regeneration. In all natural wounds a blood clot forms and starts the healing process. A natural blood clot contains [4],

- 94% Red blood cells
- 6% Platelets
- <1% White blood cells along with numerous fibrin strands.

A PRP clot instead contains [4]

- 5% Red blood cells
- 94% Platelets
- 1% White blood cells.

Components of Platelet Rich Plasma are:

1. Growth Factors
2. WBC & phagocytic cells
3. Native fibrogen concentration
4. Vasoactive and chemotactic agents
5. High concentration of platelets

Platelet Rich Plasma is an easily accessible source of growth factors to support bone and soft tissue healing and initiates a more rapid and complete healing process. It has been shown to improve the rate of bone formation and also increase the density of bone formed by 19% to 25% when measure at four months time. Because PRP is an autologous product, it also eliminates concerns about immunogenic reactions and disease transmission between individual.

Biological rationale for the use of platelet rich plasma:
Platelet rich plasma mimics the terminal stage of coagulation cascade, that is, the formation of fibrin clot. The beneficial effects of PRP are through release of certain growth factors released through α granule. Platelet Rich Plasma promotes collagen synthesis and angiogenesis leading to increased early wound strength. These peptides act both locally and systemically in a self regulatory feedback system. It is proven that PRP "jump starts" the regenerative cascade after trauma leading to quality tissue healing and patient care. The antimicrobial effect is attributed to high leukocyte concentrate. The concentration of these factors tapers by 7 days. The rate of healing is proportional to the number of platelets in the clot within graft/wound and PRP increases that initial platelet number.

.**Classification of Platelet Rich Plasma:**
They are classified as
1. Pure -Platelet Rich Plasma
2. Leukocyte -Platelet Rich Plasma

1. Pure Platelet-Rich Plasma (P-PRP) or Leukocyte-Poor Platelet-Rich Plasma– products are preparations without leukocytes and with a low density fibrin network after activation.

- Per definition, all the products of this family can be used as liquid solutions or in an activated gel form. It can therefore be injected (for example in sports medicine) or placed during gelling on a skin wound or suture (similar to the use of fibrin glues).
- Many methods of preparation exist, particularly using cell separators (continuous flow plasmapheresis) from haematology laboratory as suggested by many authors, even if this method is much too heavy to be used frequently and easily in daily practice.
- One largely advertised method of P-PRP is known under the commercial name PRGF [5] [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. Significant issues of the technique are its lack of ergonomics and the need for approximate pipetting steps during the preparation. The literature on this technique remains very difficult to evaluate, as most articles were produced by the company promoting it.
- Another technique of P-PRP was widely promoted for skin ulcers and is known under the commercial name Vivostat PRF (Platelet-Rich Fibrin, Vivostat A/S, Alleroed, Denmark), what can be a source of confusion as this technique is not a PRF following the terminology, but clearly a P-PRP product.

2. **Leukocyte-and Platelet-Rich Plasma (L-PRP)** products are preparations with leukocytes and with a low-density fibrin network after activation. Per definition, like the P-PRP, all the products of this family can be used as liquid solutions or in an activated gel form. It can therefore be injected (for example in sports medicine) or placed during gelling on a skin wound or suture (similar to the use of fibrin glues).

- It is in this family that the largest number of commercial orexperimental systems exists with many interesting results in general surgery (orthopaedic and sports medicine) [6].
- Particularly many automated protocols have been developed inthe last years, requiring the use of specific kits that allow minimum handling of the blood samples and maximum standardization of the preparations, for example Harvest Smart-PreP (Harvest Technologies, Plymouth, MA, USA) and Biomet GPS III (Biomet Inc., Warsaw, IN, USA).
- Other kits with more handling also exist, such as Plateltex(Prague, Czech Republic) or Regen PRP (RegenLab, Le Mont-sur-Lausanne, Switzerland).

Various growth factors seen in Platelet Rich Plasma:
Platelet Rich Plasma contains various growth factors. These growth factors are released when the platelets from PRP degranulates. The growth factors are released by the degranulation of alpha granules of the platelets. Various growth factors that are present include**:**
1. Platelet derived growth factor-PDGF-AA, AB, BB
2. Transforming growth factors-TGF-alpha, beta
3. Epidermal growth factor-EGF-acidic, basic
4. Fibroblast growth factor-FGF
5. Insulin like growth factor-IGF-I
6. Platelet derived epidermal growth factor-PDEGF
7. Platelet derived angiogenesis factor- PDAF
8. High concentration of leucocytes for microbicidal events
9. High concentration of wound macrophage and other phagocytic cells for biological debridement.
10. Histamines, serotonin, Adenosine diphosphate (ADP), thromboxane A2 and other vasoactive and chemotaxic agents.
11. High platelet concentration and native fibrinogen concentration for improved haemostasis.

The following will be the description of each growth factor and the role they play in repair and reconstruction

1. Platelet derived growth factor-PDGF-AA,AB,BB:

Uses in periodontal reconstruction:

- Mitogenesis increase in the number of healing cells [7].
- Angiogenesis-generating new capillaries [8].
- Up regulation of other growth factors and cells in promotion of fibroblastic and osteoblastic functions, promotion if cellular differentiation and acceleration of the effects of growth factors on other cells such as macrophages [8].
- Increase in the rate of proliferation of stem cells [9].

2. **Transforming growth factors-TGF-beta:[10]**

- TGF beta is a multifactorial cytokine that regulate growth, proliferation, adhesion and apoptosis of various cell types. In vitro enhances collagen gel contraction thereby indicates its potential in induction of fibrosis.

- TGF beta also forms substrates with glycosaminoglycans of different composition and is an important signal in regulation of integrins thus affecting cellular behaviour in adhesion, aggregation and migration.
- TGF beta that was applied in conjunction with implant placement in extraction sockets failed to increase the rate of Osseo integration
- The most important functions of TGF beta 1 and TGF beta 2 seem to be chemotaxis and mitogenesis of osteoblast precursors and the ability to stimulate their deposition of collagen matrix for connective tissue wound healing and wound formation.

3. **Epithelial Growth Factor- (EGF):**
   - Released during platelet aggregation and induces replication and migration of cells.
   - Stimulate reepithelization, angiogenesis and collagenases activity [10].

4. Fibroblast Growth Factor- (FGF)
   - Stimulates the proliferation of endothelial cells, fibroblasts, vascular smooth muscle cells, skeletal muscle myoblasts and some forms of epithelial cells. There are nine different forms of this peptide, each with its own gene. The major forms are [10]
     - FGF (acidic) –acidic: a FGF
     - FGF (basic) – basic: b FGF

     Each of them has different biological effects
     Effects- Stimulates angiogenesis, endothelial proliferation, collagen synthesis, wound contraction, matrix synthesis & epitheliazation [10].

5. Insulin Like Growth Factor (IGF):[8,10]
   - Secreted by osteoblasts during bone formation to increase numbers of osteoblasts and thereby accelerate bone deposition.
   - Systemic application of IGF-I ,rapidly activated bone turnover with an increase in serum osteocalcium and carboxy terminal propeptide of collagen I as a marker of bone formation as well as an increased urinary ratio of calcium/creatinine and desoxypyridinoline excretion- a marker of increased bone resorption.

Preparation of Platelet Rich Plasma:

Platelet rich plasma made from autologous blood is used to deliver growth factors in high concentrations to the site of the bone defect. Various methods are now available for collection of platelets.PRP obtained from gradient density cell separator by discontinuous cell separation method[8].The use of platelet concentrates obtained from this method is limited by:

1. High levels of cardiovascular stress, they produce in elderly patients
2. High production costs. To overcome these difficulties PRP are commercially available and they are
   - Curasan PRP kit
   - PCCS PRP system.

PRP can be prepared by two techniques:

1. General-purpose cell separators
2. Platelet-concentrating cell separator

As the blood is centrifuged it is separated into 3 basic components. From the least dense to the most dense and they are [8]

- Platelet poor plasma
- Platelet rich plasma called as “buffy coat”
- Dense red blood cells

Platelet poor plasma: It is the top level of serum containing autologous fibrinogen. It’s poor in platelets, acellular plasma which accounts for about 200ml of volume [8].

Platelet rich plasma: It is the second level of serum with a concentrated number of platelets and white blood cells. It contains autologous fibrinogen and accounts for 70ml of volume [8].

Red blood cells- Red coloured fraction of the second level mainly containing, packed red blood cells and platelets. Usually the upper 6-7mm are very rich in fresh, young platelets. Below this level the platelet concentration decreased and accounts for 200ml of volume.

Both the PPP and PRP contain Fibrinogen and Clotting factors.

The preparation and processing of PRP is quite similar in most of the platelet-concentrating systems although the anticoagulant used and the speed and duration of centrifugation may differ with different systems.

1. Venous blood is drawn into a tube containing an anticoagulant to avoid platelet activation and degranulation.
2. The first centrifugation is called "soft spin".
3. Separation into three layers, namely bottom-most RBC layer (55% of total volume), topmost acellular plasma layer called PPP (40% of total volume), and an intermediate PRP layer (5% of total volume) called the "buffy coat".
4. Using a sterile syringe, the operator transfers PPP, PRP and some RBCs into another tube without an anticoagulant.
5. This tube will now undergo a second centrifugation, which is longer and faster than the first, called "hard spin". This allowsthe platelets (PRP) to settle at the bottom of the tube with a very few RBCs, which explains the red tinge of the final PRP preparation. The acellular plasma, PPP (80% of the volume), is found at the top.
6. Most of the PPP is removed with a syringe and discarded, and the remaining PRP is shaken well.
7. This PRP is then mixed with bovine thrombin and calcium chloride at the time of application. This results in gelling of the platelet concentrate. Calcium chloride nullifies the effect of the citrate anticoagulant used, and thrombin helps in activating thefibrinogen, which is converted to fibrin and cross-linked [3].

On analysis of these two methods, the PCCS method is better and not only on the basis of results but also because of the ease of handling clinically and the advantages includes:

- The end products have a higher platelet count which is considered a criterion for the quality of PRP
- The platelet collection efficiency is higher so the surgeon can use more of the drawn thrombocytes.
- The volumes of PRP produced by the PCCS method is sufficient for most dento-alveolar procedures, using Curasan method ,up to 10 monovettes are required to produces an equal volume of PRP even more would be necessary to achieve the same quality of platelets and this would increase the number of working steps during PRP production.
- The preparation time needed is shorted using PCCS than using the Curasan method.
- The PCCS is a needle free system. Once the doctor has drawn the blood there is no risk of injury to the staff from contaminated needles
- PRP preparation using PCCS is more standardized and needs less training, diminishing the possibility of mistakes by staff [11, 12].

Mechanism of action of Platelet Rich Plasma:

- PRP works via the degranulation of the α granules in platelets, which contain the synthesized and pre-packed growth factors. The active secretion of these growth factors is initiated by theclotting process of blood and begins within 10 minutes after clotting. More than 95% of the presynthesized growth factors aresecreted within 1 hour. Therefore, PRP must be developed in an anticoagulated state and should be used on the graft, flap, or wound, within 10 minutes of clot initiation [13].
- The secreted growth factors immediately bind to the external surface of cell membranes of cells in the graft, flap, or wound via transmembrane receptors.
- These transmembrane receptors in turn induce an activation of an endogenous internal signal protein, which causes the expression of a normal gene sequence of the cell such as cellular proliferation, matrix formation, osteoid production, collagen synthesis etc. Thus PRP growth factors act through the stimulationof normal healing, just much faster [14].

The importance of this knowledge is that the PRP growth factors never enter the cell or its nucleus, they are not mutagenic. Therefore, PRP has no ability to induce tumor formation and has never done so.

Clinical Benefits of Platelet Rich Plasma:

- Because PRP enhances osteoprogenitor cells in the host bone and in bone grafts [13,14] it has found clinical applications in fully autogenous bone grafts and composites of autogenous bone grafts with a variety of bone substitutes with as little as 20% autogenous bone.
- Therefore, PRP has shown improved results in continuity defects[13,14]. sinus lift augmentation grafting [15,16] horizontal and vertical ridge augmentations, ridge preservation grafting [17] and periodontal/peri-implant defects [18].
- PRP was observed to allow earlier implant loading and improved osseointegration when used in compromised bone such as osteoporotic bone and bone after radiotherapy.
- Because PRP also enhances soft tissue mucosal and skin healing, it is used in connective tissue grafts, palatal grafts, gingival grafts, mucosal flaps together with Alloderm (BioHorizons, Birmingham, AL) for root coverage, skin graft donor and recipient sites, dermal fat grafts, face lifts, blepharoplasty, and laser resurfacing surgery.

Effects of PRP Growth Factors on Cells Involved in Periodontal Wound Healing:

As in other parts of the skeleton, hormones and growth factors play important roles in the development of the maxillofacial region. Various studies have examined the effects of systemic hormones and growth factors on bone and soft-tissue metabolism.

- In particular, growth factors regulate cellular events in wound healing, such as proliferation, differentiation, chemotaxis and morphogenesis of tissues and organs [10, 19].
- Growth factors may act in an autocrine, paracrine or endocrine manner. They are deposited in the extracellular matrix and are then released during matrix degradation. Their interaction with surface receptors on the target cells activates an intracellular signalling pathway that induces transcription of the messenger RNA and proteins needed for the regenerative process.
- These growth factors, in combination with other transcription factors, then activate a set of genes. The growth factors also induce specific changes at the cellular level.
  All of these effects are controlled by feedback mechanisms involving binding proteins and other growth factors [10, 19]. At a more specific level, periodontal wound healing involves gingival fibroblasts, gingival epithelial cells, periodontal ligament fibroblasts and osteoblasts, all of which are important for tissue repair and hard-tissue regeneration. A series of well-orchestrated cell–cell interactions is initiated after injury. Disruption of the vasculature as a result of injury leads to fibrin formation and platelet aggregation.
- Several growth factors are then released into the tissue from the platelets and from the adjacent cells after injury, including platelet-derived growth factor (PDGF), transforming growth factor-alpha, transforming growth factor-beta (TGF-b) and insulin-like growth factor I (IGF-I).Bone and cementum may also release growth factors during wound healing [19].
  Periodontal and oral surgical techniques may involve use of these factors in both soft and mineralized tissues [10, 19].
- For example, local application of growth factors is used to promote healing, especially regeneration.

Numerous studies, including some dental research, have shown that PDGF, TGF-b and IGF-I are found in PRP and, because of their impact on wound healing, the use of these factors has led to promising results.

Major benefits of PRP:

1. Nontoxic to tissues.
2. Easily and readily available
3. Accelerates endothelial, epithelial and epidermal regeneration
4. Stimulates angiogenesis and enhance collagen synthesis
5. Promotes enhanced soft and hard tissue wound healing
6. No risk of transmission of infectious diseases.

Limitations: [2]

• Concern over the use of bovine thrombin, bovine factor Va maybe a contaminant in certain bovine thrombin commercial preparations, antibodies to bovine factor Va may cross react with human factor Va and may produce coagulopathies and rare bleeding episodes.

• Lack of uniformity in PRP preparation protocol as different platelet concentrations have different storage time.

Safety Concerns of PRP:

- Because it is an autogenous preparation, PRP is inherently safe and therefore free from concerns over transmissible diseases such as HIV, Hepatitis, West Nile fever, and Cruetzfeld-jacob disease (CJD) ("mad vow disease") [2].
- However, Sanchez et al2003 [20] have elaborated on the potential risks associated with the use of PRP. The preparation of PRP involves the isolation of PRP after which gel formation is accelerated using calcium chloride and bovine thrombin. It has been discovered that the use of bovine thrombin may be associated with the development of antibodies to the factors V, XI and thrombin, resulting in the risk of life threatening coagulopathies.
- Bovine thrombin preparations have been shown to contain factor V, which could result in the stimulation of the immune system when challenged with a foreign protein.
- Marx et al 2004 [2] in their article stated that the second set of bleeding episodes in the patients who developed coagulopathies were not due to antibodies against bovine thrombin or human thrombin but instead due to antibodies that developed to bovine factor Va that was a contaminant in certain bovine thrombin commercial preparations.
- Other methods for safer preparation of PRP include theutilization of recombinant human thrombin, autologous thrombin or perhaps extra-purified thrombin.

The use of Platelet Rich Plasma in periodontal surgery:

- The growth factors present in PRP are capable of forming afibrin clot, promoting fibroblast proliferation and up regulating collagen synthesis in the extracellular matrix [21]. Thus, the use of PRP at injury sites might be able to promote wound healing and theregeneration of periodontal soft tissues.
- Moreover, the ability of these factors to accelerate bone repair by increasing the mitosis of osteoblasts & tissue vascularity might be useful in the treatment of infrabony defects [22]. However, the therapeutic efficacy of PRP in periodontal therapy still remains controversial.

Role in implants:

- The successful osseointegration of an implant depends on theinitial cascade of events and PRP is crucial in enhancing this outcome as PRP when coated on the surface of an implant releases an array of growth factors which enhance the early wound healing providing an initial stabilization for the implant [23].
- Role of PRP in implant therapy to provide adhesion andtensile strength for wound stabilization and sealing is of critical importance to osseointegration itself. Attachment & stabilization of the blood clot to the surface of the dental implant facilitates the migration of bone cells to the implant surface. This results in contact osteogenesis, a process that completely determines the percentage of bone implant contact.

Enhancing osseo-integration:

When an implant is to be placed with an immediate or delayed approach, the activated PRP solution is delivered into the socket or osteotomy preparation and then the implant is delivered to sink its full depth. The growth factors enriched blood clot fills the spaces in between the implant & the osteotomy walls direct application of PRP to the implant surface may disrupt or pull away the clot from the implant surface when the fixture is placed [23].

Alveolar ridge preservation:

For an immediate placement, particulate bone graft can bemixed with PRP. This facilitates graft material delivery to the site. After the condensation to the site, few drops of activated PRP are added additionally, to ensure the saturation of the implant body, the graft material and the socket walls, to reestablish the fibrin network within the graft that is disrupted during graft delivery & condensation [23].

Role in Pediatric dentistry:

Platelet concentrates have made their mark felt in pediatric dentistry also. PRP was found to be much superior to routinely used calcium hydroxide in pulp capping procedure based on the tissue reaction between these materials. PRP was found to be an ideal material with low toxic effect and increased tissue regenerating properties showing enhanced clinical results.

Effect of PRP on Regeneration:

As a whole, PRPs are considered to increase the proliferation ofosteoblasts in various cell models [24], even if the contrary was also proven while their effects on differentiation are dependent on the culture conditions. Even if the in vitromechanisms are far from being

understood in details, the effects of PRP on cells in culture are also deeply modulated by the type of bone graft biomaterial used in combination. The questionings concerning the effects of PRPs on bone healing are then difficult to answer, since they are deeply interlinked with the nature of the supporting bone biomaterial, which can be of many different kinds: autologous ,xenogeneic , allogeneic or synthetic. Many in vivo data were collected in various animal models with various PRPs alone or in association with various bone biomaterials. Some authors concluded that PRP gels have no impact on bone regeneration alone or in association with autologous bone graft, allograft, xenograft (such as anorganic bovine bone) or synthetic materials (such as β TCP). On the contrary, other authors concluded that these PRP gels stimulate significantly bone healing in association with autologous bone [25], allograft , xenograft (such as anorganic bovine bone) [26], synthetic materials (such as βTCP) or a combination of different materials. These results seemed therefore exactly contradictory.

The first systematic review that evaluated the effect of PRP on clinical applications in dentistry reported beneficial effects of PRP in the treatment of periodontal defects and it was observed that differences in treatment effects for periodontal defects in terms of clinical attachment level (CAL) were significant (ranging from 0.8 to 3.2 mm). The reported effects of PRP in sinus elevation (compared with their controls) were <10%. Evidence for beneficial effects of PRP in the treatment of periodontal defects was observed. Evidence for beneficial effects of PRP in sinus elevation appeared to be weak. No conclusions can be drawn about other applications of PRP in dentistry [27]. Another systematic review that evaluated the effect of a PRP adjunct in the treatment of intra-osseous defects underlined the limits and the heterogeneity of the available data and cautiously concluded that the specific selection of the graft type and the surgical procedures combined with PRP may be important [28].

Effect of PRP on Gingival recession:

A subsequent systematic review also evaluated the effect of PRP in various regenerative procedures of periodontal defects and gingival recession, and concluded that PRP may be advantageously used as an adjunct to grafting procedure treatments for intrabony defect but not for gingival recession [29]. This review also suggested that the use of PRP is ineffective when the GTR procedure is used for treating intrabony defects.

Effect of PRP on Soft tissue, Bone and Implant surgery:

In the field of bone tissue surgery, Wojtowicz et al [30] compared the effects of stimulating the osteogenesis of the alveolar bone by transplants of autologous bone marrow and PRP. It was shown that newly formed bone increased under the influence of PRP. PRP has also been used in sinus lift procedures, where mixed results have come out. Poeschl et al [31] showed successful results in maxillary sinus augmentation. The preparation of PRP, as applied to an implant surface, adheres to metal and might create a new dynamic surface which could potentially show biological activity. Anitua in 2006 [32] observed that osseointergation was found to be improved by coating the implant surface. Similar results were found in a recent study by The results of these studies demonstrate that PRP is effective in soft tissue healing and bone regeneration. PRP is used in bone regeneration after fractures; augmentation and even the reconstruction after jaw surgeries have shown strong effect of PRP on these treatment modalities. The combination of PRP application with other biomaterials seems to be promising as regards sinus lifting, but the results depend on the material used. Promising results have also been obtained in implant surgery, using PRP on its own as a coating material.

Platelet rich plasma contains factors, such as fibrin, fibronectin and vitronectin, that modulate important biological activities for wound healing [33]. Platelet-rich plasma has been used in different therapeutic approaches, such as sinus floor elevation, alveolar ridge augmentation, mandibular reconstruction, maxillary cleft palate repair and in the treatment of periodontal defects. However, contradictory results have been reported in bone regeneration because the detailed mechanism of its function remains unknown. Moreover, recent studies have evaluated the effect of platelet rich plasma on the formation of bone tissue, showing that this platelet concentrate may even decrease osteoconductivity in vivo [34]. It is still uncertain which concentrations of platelet rich plasma are optimal for promoting wound healing. It has been assumed that platelet-rich plasma would act in a similar manner to individual growth factors and that preparations containing maximal concentrations of growth factors are ideal. Nevertheless, this concept has not yet been demonstrated. An important issue that also deserves further study comes from the observation that growth factors are not released at the same time following platelet activation [35, 36]. Therefore, the different protocols used to obtain platelet concentrates should be studied in great detail. Platelet-rich plasma has been used, alone or in combination with stem cells, in several experimental models to promote soft and hard tissue regeneration [37]. Platelet-rich plasma has been reported as a mitogenic factor for mesenchymal stem cells from bone marrow, osteoblasts, gingival fibroblasts and periodontal ligament cells [38,39]. This positive effect is concentration specific and maximal concentrations are not necessarily associated with optimal outcomes. Therefore, further studies are needed to identify the optimal concentrations of platelet derived preparations that are necessary to promote tissue regeneration.

CONCLUSION

Platelet poor plasma has demonstrated interesting results in the field of soft tissue regeneration where they might promote myofibroblastic differentiation, cell migration and extracellular matrix remodelling. More studies are required to evaluate the role of platelet-rich and platelet-poor plasma in the regeneration of hard tissues, including alveolar bone and root cementum.

REFERENCES

1. Freymiller EG, Aghaloo TL. Platelet-Rich Plasma: Ready or Not? J Oral Maxillofac Surg 2004;62;484-88.
2. Marx RE. Platelet-rich Plasma. Evidence to support its use. J Oral Maxillofac Surg 2004;62;489-96.
3. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg 1997;55;1294–1299.
4. Marx RE. PRP; What is PRP and what is not PRP? Implant dent 2001;10 (4);225-228.
5. Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 2007;28:4551-4560.
6. Yuan T, Guo SC, Han P, Zhang CQ, Zeng BF. Applications of leukocyte- and platelet- rich plasma (L-PRP) in trauma surgery. Curr Pharm Biotechnol. 2012;13:1173-1184.
7. Kim SG,Kim WK, Park JC, Kim HJ: A comparative study of osseointegration of Avana implants in a demineralised freeze dried bone alone or with PRP; Jour of Oral and Maxillofacial Surgery 2002 Sep;60 (9);1018-1025.
8. Samuel E.Lynch, Robert J Genco, Robert E.Marx: Quinte; Tissue engineering ;applications in Maxillofacial Surgery and Periodontics. Quintessence publishing co,inc;1999;71-82.
9. Eduardo Anitua; Plasma rich in growth factors; preliminary results of the use in the preparation of future sites for implants; Int Jour Oral Maxillofacial implants 1999; 14;529-535.
10. Schliephake H;Bone growth factors in maxillofacial skeletal reconstruction; Int Jour Oral Maxillofacial Aurgery 2002;31;469-484.
11. Gernot Weibrich ,Wilfried .K.G.Kleis.Curasan PRP kit vs PCCS PRP systems, collection methods for the preparation of PRP ; Clinical Oral Impl Rest;13;2002; 437-443.
12. Gernot Weibrich ,Wilfried KG Kleis,Gerd Hafner: Growth factor levels in the platelet rich plasma produced by two different systems; Int Jour Oral Maxillofacial Implants 2002; 17; 184-19.
13. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR,Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-646.
14. Schmitz JP, Hollinger JO. The biology of platelet-rich plasma (letter to the editor). J Oral Maxillofac Surg 2001; 59:1120.
15. Kassolis JD, Rosen PS, Reynolds MA: Alveolar ridge and sinus augmentation utilizing platelet rich plasma in combination with freeze-dried bone allograft. Case series. J Periodont 71: 1654, 2000.
16. Lozada JL, Caplanis N, Proussaefs P. Platelet rich plasma application in sinus graft surgery: Part I, background and processing techniques. J Oral Implantol 27:38, 2001.
17. Carlson NE, Roach RB Jr: Platelet rich plasma: Clinical applications in dentistry. J Am Dent Assoc 133:1383, 2002.
18. Kim SG, Chung CH, Kim YK: Use of particulate dentinplaster of Paris combination with/without platelet rich plasma in the treatment of bone defects around implants. Int J Oral Maxillofac Implant 17:86, 2002.
19. Giannobile WV. Periodontal tissue engineering by growth factors. Bone1996; 19(1 Suppl):23S–37S.
20. Sanchez AR, Sheridan PJ, Kupp LI. Is platelet rich plasma the perfect enhancement factor? A current Review. Int J Oral Maxillofac Implants 2003;18:93-103.
21. Kawase T, Okuda K; Platelet-rich Plasma-derived Fibrin Clot Formation Stimulates Collagen Synthesis in Periodontal Ligament and Osteoblastic Cells in Vitro. J Periodontol 2003; 74: 858–864.
22. Kanno T, Takahashi T; Platelet-rich Plasma Enhances Human Osteoblast-like Cell Proliferation And Differentiation. J Oral Maxillofac Surg 2005;63:362–36.
23. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet‑rich plasma (PRP)in dental and oral surgery: From the wound healing to bone regeneration. Immun Ageing 2013;10:23.
24. Creeper, F.; Lichanska, A.M.; Marshall, R.I.; Seymour, G.J.;Ivanovski, S. The effect of platelet-rich plasma on osteoblast and periodontal ligament cell migration, proliferation and differentiation. J. Periodontal Res., 2009, 44(2), 258-265.
25. Fennis, J.P.; Stoelinga, P.J.; Jansen, J.A. Mandibular reconstruction: a histological and histomorphometric study on the use of autogenous scaffolds, particulate cortico-cancellous bone grafts and platelet rich plasma in goats. *Int.* J. Oral Maxillofac. Surg., 2004, *33*(1), 48-55.
26. Torres, J.; Tamimi, F.; Tresguerres, I.F.; Alkhraisat, M.H.; Khraisat, A.; Blanco, L.; Lopez-Cabarcos, E. Effect of combining platelet-rich plasma with anorganic bovine bone on vertical bone regeneration: early healing assessment in rabbit calvariae. Int. J. Oral Maxillofac. Implants, 2010, *25*(1), 123-129.
27. Plachokova AS, Nikolidakis D, Mulder J, Jansen JA, Creugers NH. Effect of platelet-rich plasma on bone regeneration in dentistry: a systematic review. Clinical Oral Implants Research2008;19(6):539–45.
28. Kotsovilis S, Markou N, Pepelassi E, Nikolidakis D. The adjunctive use of platelet-rich plasma in the therapy of periodontal intraosseous defects: a systematic review. Journal of Periodontal Research2010;45(3):428–43.
29. Del Fabbro M, Ceci C, Taschieri S. Systematic review on the effect of platelet concentrates for the surgical treatment of periodontal defects.Dental Cadmos2013;81(3):138–45.
30. Wojtowicz A, Chaberek S; Comparison Of Efficiency Of Platelet Rich Plasma, Hematopoieic Stem Cells And Bone Marrow In Augmentation Of Mandibular Bone Defects. NY State Dent J 2007;73:41–45.
31. Poeschl PW, Ziya-ghazvini F; Application of Platelet-rich Plasma for Enhanced Bone Regeneration in Grafted Sinus. J Oral Maxillofac Surg 2012; 70:657–664.
32. Anitua Ea; Enhancement of Osseointergation by Generating A Dynamic Implant Surface. J Oral Implantol 2006; 32:72–76.
33. Kotsovilis S, Markou N, Pepelassi E, Nikolidakis D. The adjunctive use of platelet-rich plasma in the therapy of periodontal intraosseous defects: a systematic review. JPeriodontal Res 2010: 45: 428–443.
34. Ranly DM, McMillan J, Keller T, Lohmann CH, Meunch T, Cochran DL, Schwartz Z, Boyan BD. Platelet-derived growth factor inhibits demineralized bone matrix-induced intramuscular cartilage and bone formation. A study of immunocompromised mice. J Bone Joint Surg Am 2005: 87: 2052–2064
35. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat M, Van Dyke TE. Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. J Periodontol 2007: 78: 661–669.
36. Frechette JP, Martineau I, Gagnon G. Platelet-rich plasmas: growth factor content and roles in wound healing. J Dent Res 2005: 84: 434–443.
37. Lucarelli E, Beccheroni A, Donati D, Sangiorgi L, Cenacchi A, Del Vento AM, Meotti C, Bertoja AZ, Giardino R, Fornasari PM, Mercuri M, Picci P. Platelet-derived growth factors enhance proliferation of human stromal stem cells.Biomaterials 2003: 24: 3095–3100.
38. Annunziata M, Oliva A, Buonaiuto C, Di Feo A, Di Pasquale R, Passaro I, Guida L. In vitro cell-type specific biological response of human periodontally related cells to platelet- rich plasma. J Periodontal Res 2005: 40: 489–495.
39. Graziani F, Ivanovski S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res 2006: 17:212–219.