Platelets and Their Pathways in Dentistry: Systematic Review

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INTRODUCTION

The platelets are best known for their importance in clotting blood. However, platelets also contain hundreds of proteins called growth factors which are very important in the healing of injuries. First, the platelets were used for therapeutic purpose in transfusion medicine, wherein the platelet concentrates were originally used for the treatment and prevention of hemorrhage due to severe thrombopenia, which is often caused by medullar aplasia, acute leukemia, or significant blood loss during long-lasting surgery. The standard platelet concentrate for transfusion has been named plate-rich plasma (PRP) which classically contains $0.5 \times 10^{11}$ platelets per unit.¹,² PRP is plasma with many more platelets than what is typically found in blood. The concentration of platelets and thereby the concentration of growth factors can be 5–10 times greater (or richer) than usual. To develop a PRP preparation, blood must first be drawn from a patient. The platelets are separated from other blood cells, and their concentration is increased during a process called centrifugation. Then, the increased concentration of platelets when combined with the remaining blood will have a greater concentration of growth factors than whole blood.¹ This product is being used to encourage a brisk healing response in the surgical wounds across several specialties in particular dentistry, orthopedics, and dermatology.¹,³ As a concentrated source of blood plasma and autologous conditioned plasma, PRP contains several different growth factors and cytokines which can stimulate the effective healing of both soft and hard tissues. Although blood is mainly a liquid called plasma, it also contains small solid components red cells, white cells, and platelets which have been found to play a critical role in wound healing and hemostasis as well as in repairing the bone fracture.²,³

This review will highlight the innate properties of platelets including wound healing and bone remodeling as well as a brief description about the various therapeutic uses of platelets in dentistry and other related fields. The role of platelets in dentistry is immense, and their potential benefits have led to their increased usage in various forms.

ADVANTAGES OF PRP

Platelet-rich plasma (PRP) is concentrated platelet-rich blood that has been centrifuged to concentrate the platelet population. PRP contains a variety of growth factors that are released from activated platelets and can stimulate cell proliferation, matrix remodeling, and angiogenesis. These growth factors play a critical role in the healing process, particularly in wound healing and tissue regeneration. PRP can be applied topically or injected into the wound or tissue site, allowing for the delivery of these growth factors directly to the site of injury.

INDICATIONS FOR PRP USE

PRP has been used in a variety of clinical settings to promote healing and tissue regeneration. Some of the common indications for PRP use include:

1. **Wound Healing**: PRP can be used in the treatment of chronic wounds, such as diabetic foot ulcers, pressure sores, and burn wounds. It has been shown to improve healing times and reduce the risk of infection.
2. **Orthopedic Applications**: PRP has been used in the treatment of bone fractures, tendon injuries, and ligament tears. It can help promote bone regeneration and accelerate healing.
3. **Periodontal Treatment**: PRP has been found to be effective in the treatment of periodontal disease, including periodontal ligament repair and regeneration. It can help improve bone regeneration and reduce inflammation.
4. **Soft Tissue Repair**: PRP can be used in the repair of soft tissue injuries, such as tears in the meniscus or rotator cuff. It has been shown to improve healing and reduce pain.
5. **Dentistry**: PRP has been used in dentistry to help promote healing after oral surgery, such as wisdom tooth extraction or dental implant placement. It can help reduce swelling and improve healing.

CONCLUSION

Platelets are a critical component of the healing process and play a significant role in promoting tissue regeneration. Platelet-rich plasma (PRP) has become a popular treatment option in a variety of clinical settings due to its ability to deliver a concentrated source of growth factors to the site of injury. Further research is needed to fully understand the mechanisms by which PRP promotes tissue regeneration and to identify new applications for this promising treatment option.
applications in other fields. This review is an attempt to summarize the research work updated by Dr. Anitua Eduardo since 2000 till 2016.

**Search strategy**
The methodology to update this review was based on secondary research involving library referencing from the year 2000 to 2017, through online search using keywords such as platelets, platelet concentrates, PRP, wound healing, bone remodeling, and angiogenesis.

**Discussion**

**Role of platelets in wound healing**
Platelets and macrophages are thought to be dominant regulatory cells in wound healing.⁶,⁷ Activated platelets release locally acting growth factors that initiate division and migration of fibroblasts and formation of new capillaries. Wound healing has been found to be under the control of two processes, angiogenesis and collagen synthesis, which are the expected immediate host’s reaction to any tissue injury. The normal wound healing process involves the activated fibroblasts at the wound healing site to divide and produce collagen along with intense capillary proliferation to provide nutrients for the increased cellular activity. Although the exact signaling mechanism still remains elusive, it is debated that the coagulation product itself would enhance the further coagulation. Platelets activated by thrombin release a mitogen (platelet-derived growth factor [PDGF]) for fibroblasts and smooth muscle cells (SMCs) and stimulate increased collagen synthesis by smooth muscle although the neutrophils are the predominant inflammatory cell in the traumatic central dead space of the wound from the 1st to 3rd day following injury. However, macrophages gradually replace the neutrophils 3–4 days after wounding and remain in the central dead space of the wound until repair is complete. Macrophages produce growth factors that stimulate neovascularization, fibroblast proliferation, and migration. It was Matras in 1972 who had first used platelets as sealants to promote homeostasis for surgical procedures. He also had demonstrated the importance of fibrin in reuniting human nerves with the aid of concentrated levels of fibrinogen and factor XIII. Gibble *et al.* in 1990, provided the initial evidence for the potentiality of this approach, and years later, Marx *et al.* using the technique of gradient density centrifugation produced PRP with the aim of enhancing the functionality of the bone grafts.⁶,⁷ The autologous platelet products have high therapeutic potential and therefore can be used in various formulations and in various fields of medicine and tissue engineering. Several key biological factors have been found in PRP which are directly involved in tissue repair including insulin-like growth factor type I (IGF-I), Transforming Growth Factor Beta 1, PDGF, hepatocyte growth factor, vascular endothelial growth factor (VEGF), and basic fibroblastic growth factor among others.⁸,⁹ PRP contributes to hemostasis by preventing blood loss at sites of vascular injury as they contain a large number of growth factors and cytokines that have a key role in bone regeneration and soft tissue maturation. In the past two decades, an increased understanding of the physiologic roles of platelets in wound healing after tissue injury has led to the idea of using platelets as therapeutic tools. Platelet concentrate is activated by way of thrombin generation with calcium which is a three-dimensional and biocompatible fibrin scaffold resulting in progressive release of a myriad of growth factors and proteins to the local environment thus contributing to the accelerated postoperative wound healing and tissue repair [Figure 1]. Eventually, autologous PRP as a novel therapeutic alternative has opened up new avenues in other fields including orthopedics, sport medicine, dentistry, periodontal surgery and plastic and maxillofacial surgery, where it creates biological safe environment for an effective and rapid wound healing and tissue repair or regeneration.⁸,⁹

**Molecular control and signaling involved in wound healing process**
As a result of hemostatic response to an external injury, restoration of the integrity of the vascular wall takes place which involves orchestrated proliferation and migration of SMCs, fibroblasts, and endothelial cells for which platelets, growth factors, and chemokines are involved.
known to contribute to regulate these processes. The migration and proliferation of SMCs in both the arterial and venous circulation is found to be regulated by PDGF which contributes effectively during hemostasis and tissue healing. Another important mediator in healing and remodeling is platelet-derived stromal cell-derived factor 1α (SDF-1α) which mediates CD34+ bone marrow-derived progenitor cells to the injury site and promote their differentiation into endothelial progenitor cells. Since inhibition of SDF-1α binding to its receptor CXCR4 was shown to retard diabetic wound healing in experimental models by impairing cellular migration while concomitantly prolonging the inflammatory response supports the role of SDF-1α in tissue healing. In addition to angiogenic factors, platelets also store and secrete a number of tumor necrosis factor-α-related apoptosis regulators such as CD95, Apo-L, and Apo3-L which can bring about apoptosis in other circulating cells as well as in antiapoptotic molecules. Thus, the balance between proapoptotic and antiapoptotic molecules adequately promoting survival or eliminating the cells from the wound site is also crucial for regulation of wound healing. It can therefore be concluded that an in-depth understanding of platelets and their secretions in wound healing and tissue regeneration has led to applications of platelets in multiple fields especially in trauma management [Table 1].

**Role of platelets in bone remodeling**

The effects of platelets on bone can be viewed within the frames of bone formation and resorption. Platelets act in both the processes. In acute conditions such as bone fractures, fracture site is surrounded by activated platelets and their aggregates. Degranulation of activated platelets leads to the release of several growth factors (e.g., PDGF, VEGF, IGF-1, IGF-2, EGF, and TGF-B). Degranulation of activated platelets leads to the release of several growth factors (e.g.; PDGF, VEGF, IGF-1, IGF-2, EGF and TGF-B), all contributing to the recruitment of osteogenic cells after tissue injury. Platelets release also contains mediators, which may be involved in the bone remodeling (e.g., thromboxane A2 and prostaglandins). The supportive effect of platelets on bone formation was reported in several in vitro and clinical studies where it has been reported that PDGFs promote bone formation by influencing cell proliferation, chemotaxis differentiation, and extracellular matrix synthesis. Some in vitro studies confirmed the contribution of platelets in osteoclastogenesis and bone resorption, but no exact mechanism has been proposed yet. The multidimensional effect of the platelet on bone resorption and bone formation represent a dilemma, as on the one side, there are growth factors enhancing bone formation such as PGDF; on the other side, there

| Classification | Protein | Biological effect |
|----------------|---------|------------------|
| Adhesive properties | Von willebrand factor (vWF) propeptide, Fibrinogen, Fibronectin, Vitronectin, Thrombospordin 1 (TSP 1), Laminin-B, signal peptide-CUB-EGF domain containing protein 1 (SCUBE 1) | Cell contact interactions, homeostasis and clotting, and extracellular matrix composition |
| Clotting factors and associated proteins | Factor V/Va, factor XI-like protein, mutimerin, protein S, high-molecular weight kininogen, antithrombin III, tissue factor pathway inhibitor | Thrombin production and its regulation |
| Fibrinolytic factors and associated proteins | Plasminogen, plaminogen activator inhibitor-1 (PAI-1), Urokinase plasminogen activator (Upa), alpha 2-antiplasmin, histidine-rich glycoprotein, thrombin activable fibrinolysis (TAFI), Alpha 2-macroglobulin | Plasmin production and vascular modeling |
| Proteases and antiproteases | Tissue inhibitor of metalloprotease 1-4 (TIMPS 1-4), metalloproteases1, 2, 4, 9, disintegrin and metalloproteinases with a thrombospondin type 1, motif member 13, tumor necrosis factor - alpha - converting enzyme (TACE), protease nexin-2, C1 inhibitor, serpin proteinase inhibitor8, alpha 1-antitrypsin | Angiogenesis, vascular modeling, regulation of coagulation, and regulation of cellular behaviour |
| Antimicrobial proteins | Thrombocidins, Defensins | Bactericidal and fungicidal properties |

| PGDF | Osteoblastic proliferation |
|------|---------------------------|
| EGF  | Cooperation with RANK L with Osteoclasts differentiation |
| TGF-B | Stimulation of OPG synthesis |
| TXA2 | Induction of Osteoclastogenesis |
| PGs (E and F SERIES) | Effects on Osteoclasts function and Osteoblasts differentiation, inhibition of OPG Production |
| PGE2 | Stimulation of RANK L expression in Osteoblasts, cooperation of RANK L and M-CSF and Inhibition of Osteoclasts formation |

are EGF and TGF-B which are more likely to enhance the bone resorption. It is therefore concluded that platelets’ effect on the bone is complicated because of the complex interactions between growth factors, inflammatory mediators, and cytokines. In fact, the main effect depends on the specific endothelial
gene expression of osteogenesis and osteoclastogenesis. To be successful in bone regeneration and improving damaged bone healing, any substitute should be biologically compatible, nontoxic, and should provide scaffolding for angiogenesis [Table 2].[12]

**Role of platelets as bacteriostatic agents**

As it is learnt that growth factors are essentially involved in the regeneration process and are found to be helpful in stimulating cell proliferation (mitosis), cellular migration (chemotaxis), differentiation (morphogenetic effect), angiogenesis, and the combination of several of these effects during the tissue regeneration period. In addition to their effective control over angiogenesis and proliferation, another important property of platelets is the bacteriostatic effect. This effect has been observed against *Staphylococcus aureus* and *Escherichia coli* bacteria.[7] *Porphyromonas Gingivalis*, and *Actinobacillus actinomycetemcomitans.[13]*

**Applications of platelet concentrates in oral and maxillofacial surgery**

The clinical use of PRP may enable patients to achieve satisfactory wound healing involving both the hard and soft tissues with shorter recovery times, reduced levels of postoperative infection, edema, ecchymosis, and blood loss [Table 3].

**Novel combinations and new applications of platelet concentrates (plate-rich plasma)**

The roles played by platelets and growth factors have contributed immensely toward understanding their effectiveness in angiogenesis, chemotaxis, and cell proliferation. They are also found to be involved in controlling the synthesis and degradation of extracellular matrix and proteins by binding to the extracellular domain of a target growth factor receptor which in turn activates the intracellular translocation pathways. These findings support the use of different growth factors and cytokines as therapeutic molecules for the repair regeneration of a wide range of tissues [Table 4].

**Table 3: Applications of platelets concentrates in oral and maxillofacial surgery[14‑19]**

| Procedure | Description |
|-----------|-------------|
| Oral surgery | PRP enhances and accelerates soft tissue repair and bone regeneration |
| PRP along the fracture lines may enhance bone regeneration |
| Anitua (2006), showed that the osseointegration of implants was enhanced by coating the implant surface with PRP prior to insertion into the alveolus |
| Successful results when PRP was used in combination with a graft material in maxillary sinus augmentation |
| BRONJ (Bisphosphonate related-osteonecrosis of the jaw) | Resection of the necrotic bone with primary closure of the mucosa over the bony defect using PRP |
| The orthopanoramic and computed tomography performed before and after surgery revealed successful outcomes |
| Use of PRP enhances wound healing and reduce bone exposure and would be an effective treatment protocol to use in BRONJ subjects |
| Healing of Extraction socket | Improved soft and hard tissue healing was found |
| Pain and swelling | Reduced swelling and pain after surgical extraction of impacted third molars and more comfort post operatively |
| Soft tissue dimensional changes in surgical wounds (Decubitus or chronic ulcers) | Greater radiographic bone density , significant improvement in bone healing in third molar extraction |
| Plasma concentrate cells tend to populate surgical wound, secreting PDGF, TGF-B, VEGF |
| Tend to accelerate soft tissue healing by stimulating angiogenesis, granulation tissue formation and epithelialization along with gain in keratinized tissue formation |
| PRGF have been found useful in the treatment of chronic cutaneous ulcers |
| Hard tissue dimensional changes in surgical wounds | Less resorption of the bone post surgically |
| Alveolar cleft reconstruction | PRP seems to enhance bone formation in alveolar clefts when mixed with autologous cancellous bone harvested from the iliac crest |
| PRP and mineral trioxide aggregate (MTA) were placed into the root canal. Six months after PRP treatment, radiographical examination revealed resolution of the radiolucency and progressive thickening of the root wall and apical closure. Our findings suggest that PRP can be used for the treatment of immature permanent teeth with periapical lesion, as part of a regenerative endodontic treatment procedure |

**Platelets in combination with bone implants to facilitate the anchorage of the dental prosthesis**

studies have investigated that titanium implants when coated with PDGFs before insertion into the host tissues resulted in improved bone formation around the implant. This resulted in sufficient osseointegration of the implant and their subsequent longevity which is attributed to the release of considerable growth factors and proteins including TGF-B1, PDGF, IGF, bone sialoproteins, thrombospondin, and osteonectin. Tissue-engineered bone regeneration showed strong correlation between osseointegration and injectable bone comprising of PRP with autogenous bone and mesenchymal stem
cells (MSCs) when injected into the implant sites before installation of implant.\textsuperscript{[11]}

**Platelets concentrate for repair of the soft connective tissue**

Both *in vivo* and *in vitro* studies have confirmed that these platelet-rich matrices are safe and effective in accelerating the tendon cell proliferation, stimulating the synthesis of type I collagen and promote neovascularization.\textsuperscript{[11]}

**Platelets concentrate for cosmetic surgery**

Since the esthetic concerns have raised globally, the application of platelets and their concentrates are being used especially for the soft tissue and bony reconstructions encountered in facial plastic and reconstructive surgery. In these applications, their use has been associated with a decrease in operative time, necessity for drains and pressure dressings, and incidence of complications. Besides, its use is also documented in hair growth therapy where it promotes new hair follicles and strengthens the existing ones.\textsuperscript{[20]}

**Platelets concentrate in alveolar cleft**

It has been found that in combination with allografts and xenografts, these concentrates have demonstrated effective bone remodeling which is contributed by the wound healing and angiogenic property. This combination in future could possibly become an alternative for autogenous bone graft which requires an additional surgery and carries the risk of donor-side morbidity.\textsuperscript{[5]}

**Combination of mesenchymal stem cell and plate-rich plasma**

Combination of MSC and PRP was found to shorten the treatment time during distraction osteogenesis when injected at the surgical site consolidation phase by accelerating the bone regeneration safely and effectively.\textsuperscript{[21]}

**Platelets concentrate in combination with different bone matrices**

There are several reviews and research studies where the use of allograft and xenograft has been suggested along with platelet concentrates which would give support to the matrix and its adaptation to the injured tissue. All needed is a suitable blood supply during the repair as the inadequate blood supply would result in decreased bone volume.\textsuperscript{[22]}

**Conclusion**

Since PRP is a vehicle of mitogenic and chemotactic cytokines and growth factors, it shows to possess beneficial effects for several clinical applications and makes its use more attractive. The quintessential aim of using plasma rich in growth factors is based on the facts that such growth factors booster system will increase the local concentration of growth factors, thereby provide an effective cell-based fibrin scaffold activating the endogenous tissue regeneration mechanism and its intricate nature. However, quest of

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**Table 4: Different therapeutic applications using platelets concentrates\textsuperscript{[6,7]**

| Emerging field                  | Target                          | Result                                                                                           |
|---------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------|
| Neural regeneration             | Peripheral nerve regeneration   | Promotes regeneration of injured peripheral nerve                                               |
|                                 | Central nervous system          | Cytokines in PRGFs could be involved in the protecting neurons and glia from apoptosis          |
|                                 |                                 | Promotes axonal outgrowth and remyelination                                                    |
|                                 |                                 | PRP facilitates angiogenesis and collagen synthesis                                              |
| Ophthalmology                   | Corneal persistent epithelial   | An effective therapeutic agent for the treatment of a broad etiopathological spectrum of corneal |
|                                 | defects and ocular burns         | persistent epithelial defects as well as ocular burns                                           |
| Cardiovascular therapy          | Refractory angina               | Intramyocardial injection of autologous PRP combined with transmyocardial revascularization may be more efficacious at relieving angina |
| Dermatology                     | Burns                           | PRGF have the potential to accelerate the wound healing                                         |
|                                 | Ulcers                          | PRP favours the healing process of chronic ulcers                                               |
| Cosmetic and plastic surgery    | Facial rejuvenation/surgical    | Non-surgical reduction of wrinkles                                                               |
|                                 | intervention                    | Stop the capillary bleeding                                                                     |
|                                 | Dermal augmentation             | Platelet rich preparations provide significant long-term and potential for stimulated dermal   |
|                                 | Enhancement of regeneration of   | augmentation                                                                                     |
|                                 | substance loss                  | Platelet rich plasma and autologous adipose graft are able to regenerata the substance loss and |
|                                 | Free fat graft survival          | wound closure with a significant healing time reduction                                          |
|                                 |                                 | The infiltration of free fat graft with PRGF reduces the inflammatory reaction and increases   |
|                                 |                                 | the maintenance of the transplanted fat cells                                                   |
| Endodontics                     | Periapical tissue regeneration  | PRP could provide an ideal scaffold for the regeneration of vital tissues in a tooth with     |
|                                 |                                 | necrotic pulp and a priapical lesion                                                            |
| Cell delivery and               | Enhance cellular proliferation   | Neural differentiation of human bone marrow stem cells is enhanced over PRP                      |
| regenerative medicine           | and differentiation             | -scaffolds                                                                                        |

PRGFs=Platelet related growth factors
intense research is always encouraged to understand the intricacies of molecular mechanisms which control different biological cascades to explore novel therapeutic applications of platelets- and plasma-based technologies. The ability to understand all these challenges and pathways played by platelets and their concentrates will definitely avoid any ambiguity surrounding its clinical and therapeutic applicability so that its therapeutic benefits are extended worldwide for better treatment results.

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**Conflicts of Interest**
There are no conflicts of interest.

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