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Effectiveness of platelet rich plasma in accelerating the healing of wounds

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Abstract
Chronic and acute non-healing wounds represent a major public health problem, and replacement of cutaneous lesions by the newly regenerated skin is challenging. Platelet-rich plasma (PRP) is a widely used throughout diverse fields of medicine for improving tissue regeneration. The aim of this study was to evaluate the effectiveness of autologous platelet-rich plasma (PRP) in individuals with chronic and acute non-healing wounds. This prospective study was carried out in the Department of Orthopaedics, Rajawadi Muncipal General Hospital, Mumbai in which a total of 13 patients were enrolled.

Keywords: Chronic wounds, growth factors, wound healing, platelet-rich plasma, platelet gel

Introduction
Skin is the largest organ in vertebrates, comprising 10% of the total body mass and covers the entire surface area [1, 2]. It has a crucial role in defense and survival thanks to its self-repairing and self-renewing capacity, acting as an important barrier from the outer environment to the inner environment [3]. A disturbance of the normal anatomic structure and functional integrity of the skin can be described as a wound [4]. Wound healing is a coordinated dynamic tissue repair process, which involves the interaction of multiple cell types, growth factors, cytokines, and chemokines [5, 6]. If this mechanism is interrupted, chronic, non-healing wounds or excessive granulation tissue formation can appear, leading to arresting in the chronic inflammatory phase [7].

In recent years, the overall prevalence of chronic degenerative diseases associated with ageing has increased dramatically; in this way chronic wounds represent a significant biomedical burden. Millions of patients all over the world are affected by acute and chronic wounds as a result of surgeries, burns, infections, pressure ulcers, and diabetic and venous ulcers [4]. In the USA, more than 6 million people suffer from chronic wounds with an annual cost of $25 billion [8]. From the 150 million diabetes patients in the world, foot ulcerations that frequently develop into nonhealing wounds represent 15% [9]. Almost 2% of the health budgets in Europe are spent in chronic wound management [10]. The effectiveness of current chronic wound treatment is estimated at 50%, and are expensive as repetitive treatments are needed [11].

Despite significant advances in medical care and nutrition, there is a growing need to develop novel strategies to improve cutaneous wound healing. The medical field is rapidly advancing towards the development of low or non-invasive procedures and accelerated treatments that can achieve a reduced morbidity and a good functional recovery in our patients to improve their quality of life. In the last few years these simple and cost-efficient procedures have had a potential impact reducing economic costs for standard general medical treatments [12]. Regenerative medicine can be defined as an emerging interdisciplinary field in biomedical research that aims to restore, regenerate, and replace damaged tissues and cells [13].

Platelet-rich plasma (PRP) is an endogenous therapeutic technology that is gaining interest in regenerative medicine due to its potential to stimulate and accelerate tissue healing [14]. PRP is defined as an autologous biological product derived from the patient's blood, and in which after a centrifugation process a plasma fraction is obtained with a platelet concentration higher than that in circulating blood [15].

Platelets play a crucial role in the wound healing process thanks to their hemostatic function and presence of cytokines and growth factors [16]. There are several growth factors which are known to be involved in the wound healing process, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF1, IGF2), vascular endothelial growth factor (VEGF), transforming growth factor (TGF-_), and keratinocyte growth factor (KGF) [17–20] (Figure 1).

So far, only the PDGF has been approved by the United States Food and Drug Administration

(FDA) and by the European Authorities (EMEA) for clinical application in patients [21, 22]. Growth factors are a group of soluble and diffusible polypeptide substances that regulate growth, differentiation, proliferation, and cellular metabolism of numerous cell types [14, 23]. They promote endothelial and epithelial regeneration, stimulate angiogenesis, collagen synthesis, soft tissue healing, and hemostasis [24].

The use of growth factors to promote cutaneous wound healing has existed since the 1940s, and they can be applied in a wide range of ways, either by traditional topical or intralesional administration or by using specific scaffolds or even gene therapy [25]. Animal and human trials have reported successful PRP clinical applications for chronic skin ulcers [26, 27], acute cutaneous wounds [28, 29], burns [30], and plastic and cosmetic surgery [31, 32].

Regardless different conventional therapeutic approaches targeting wound healing enhancement, the use of novel treatments remains still a clinical challenge. There is a continued search towards regenerative therapies to reduce health care burden. *In vivo* and *in vitro* clinical and experimental studies on cutaneous wound regenerative therapies such as PRP and stem cells are providing encouraging results. For all the above mentioned reasons, this article aims to review the regenerative skin wound healing field focusing on platelet-rich plasma as a cost-effective therapeutic approach.

The Role of Growth Factors in the Wound Healing Process

Growth factors play an essential role in the complex process of wound healing and tissue regeneration [33]. They are signaling proteins that influence the metabolism of other cells [34]. Each GF has more than one effect on the wound healing process, and act by binding to specific receptors on cell membranes of target cells [35]. These effects include promoting chemotaxis (attracting cells into the wound), inducing cell migration and proliferation, and stimulate cells to upregulate protein production [36]. These GFs not only regulate cell migration and proliferation, but also remodel the extracellular matrix and promote angiogenesis, creating an ideal environment that favours the cutaneous wound healing process [37].

Almost every cell type in skin is involved in the production of GFs and several cells release many different types of GFs during the wound healing process [38].

Through degranulation of the alpha granules in platelets, PRP can secrete various GFs, including PDGF, VEGF, FGF, hepatocyte growth factor (HGF), and TGF_, which have been documented to initiate wound healing process [39].

The main GFs which are currently known to be involved in the wound healing process are PDGF, EGF, FGF, IGF, VEGF, TGF_, HGF, and KGF [18]. Their roles on the wound healing process are described in the following sections.

Platelet Rich Plasma: Preparation Methods and Therapeutic Formulations

Platelet-rich plasma can be defined as a fraction of plasma containing higher concentrations of platelets compared to whole blood and as a result an increased growth factor concentration [40]. Nowadays, PRP is widely applied in different clinical applications to promote healing in orthopaedics [41], soft tissue healing [42], nervous tissue [43], chronic skin ulcers [44], ophthalmology [45], and dentistry [46]. PRP is categorized by the Food and Drug administration (FDA) as aminimally-manipulated tissue and as an autologous blood product [47]. One of the advantages of these preparations is that they are easily obtained from the patient's blood after a simple centrifugation process, thus, it is a safe, simple, and cost-effective product [48, 49]. By controlling centrifugation parameters and the activation protocol, it is possible to control the dose of GFs and proteins that are released upon activation [50]. At the moment, there is no clear gold standard protocol for PRP generation, little characterization performed on the obtained products and lack of regulation and standardisation [48]. To characterize the main components that play a key role in tissue regeneration and formulate an adequate preparation for each specific pathophysiological situation, a well-defined simple procedure is necessary, where centrifugation conditions are fundamental to obtain a high PRP quality together with quantification and identification of platelets and lymphocytes [48, 51].

In recent years there has been significant controversy regarding the nomenclature and definition of PRP [52, 53]. According to Anitua and colleagues (2007), the nomenclature "platelet-rich plasma" is a vague and imprecise term. There is a large number of autologous blood preparations that differ regarding their processing protocols and preparation and, therefore, in quantitative and qualitative characteristics. Therefore, a detailed, precise, and stepwise description of the PRP preparation protocol (centrifugation conditions, platelet concentration, type of anticoagulant used, platelet activator and presence or absence of leukocytes) is required to allow a comparison in between studies.

Moreover, it is important to preserve platelet integrity and quality preventing damage or lysing of platelets to allow them to fully secrete growth factors. As a result of all the above mentioned reasons, an advanced autologous PRP system was developed by the Biotechnology Institute, BTI, the Plasma Rich in Growth Factors, known as PRGF-Endoret. It is certified by European health authorities and has been approved in Europe for the production of PRP and their application in several medical fields. PRGF is an autologous product with a moderate concentration of platelets, absence of leukocytes and provides the formation of a biological scaffold formed by fibrin for cell adhesion which will help the wound healing process. The mentioned technology together with other PRP preparation methods are described in the following sections.

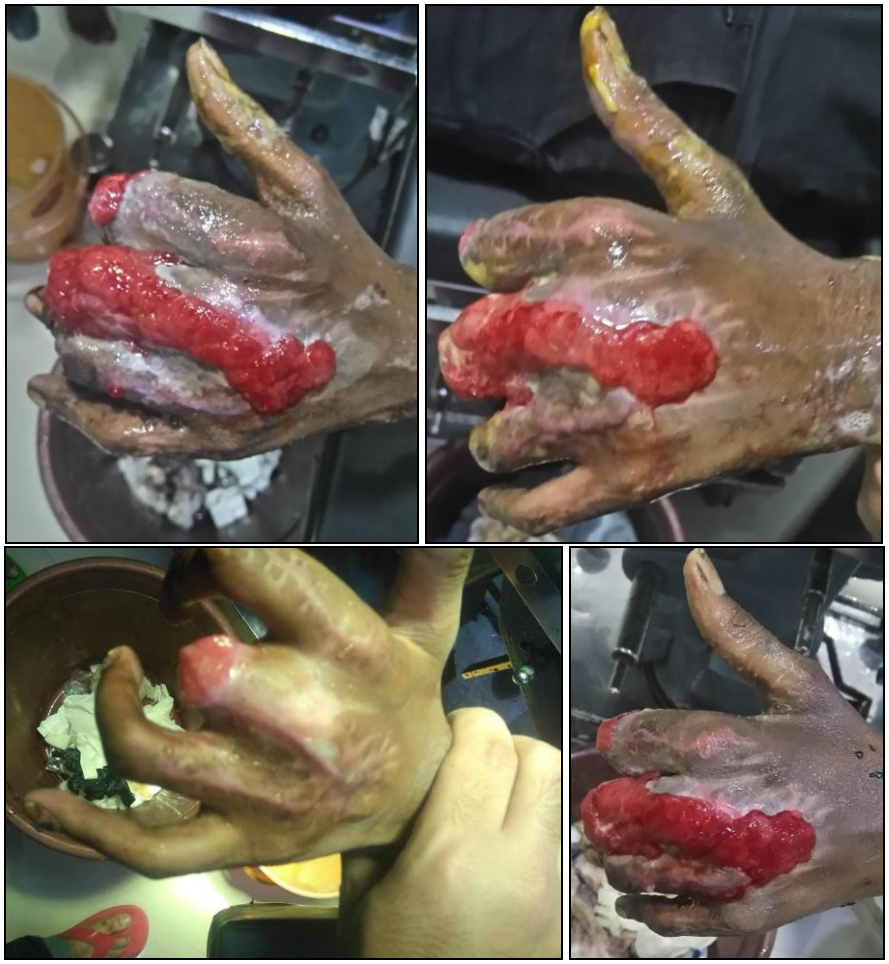

Fig 1: Clinical picture

Preparation Methods

Within the existing methods for the preparation of PRP there is discrepancy in technical details, such as the inclusion of leukocytes or red blood cells, speed, and time of centrifugation. Although it seems that the results are similar [54]. Anitua (2004) defends the non-inclusion of leukocytes, because they can alter the function of some GFs and interfere in the anti-inflammatory action [55]. Others, such as the Harvest Technologies corporation, claims that these details are not important and that their PRP contains some red blood cells. Moreover, other authors prefer the inclusion of leukocytes for the treatment of ulcers or other surgeries, since they consider that it has an antimicrobial effect [56, 57].

The Use of Platelet-Rich Plasma in Cutaneous Wound Healing

Over the last decades, the use of emerging cellular therapies, such as PRP, has gathered more attention in a wide range of diseases and settings for its potential use in the regenerative medicine field as a therapeutic agent and can have an adjunctive role in a standardized, quality treatment plan [58]. The medicine field is advancing towards the development of less-invasive and cost-effective treatments to enhance functional recovery [51]. The use of PRP has had a potential impact in reducing economic costs for standard medical treatments, although it should not be considered as a therapy that replaces certain essential conventional treatments, such as debridement of necrotized tissue, but as a complementary therapy [51, 59]. A biological internal environment for tissue homeostasis restoration is created with PRP therapy by providing to the wounded area several signalling cytokines and growth factors which play a crucial role in tissue repair process by regulating inflammation, stimulating angiogénesis, and synthesis together with the remodelling of new formed tissue [58, 60].

Additional advantages of PRP treatment in cutaneous wound healing includes easy methodology, cost-effective treatment, more lasting effect compared to conventional therapy, and safe treatment being at autologous product obtained from the own patient [61, 62].

The use of PRP in both humans and animals is steadily increasing, and its healing properties in cutaneous wounds have been reported in many clinical and experimental studies with dogs [63, 64], horses [65], humans [60, 66], and other species [29, 67]. Platelets play an important role in the wound healing process thanks to hemostatic functions and concentrated levels of growth factors and cytokines [68]. A higher concentration of growth factors promotes the regeneration of epithelial and endothelial cells, stimulates angiogenesis, collagen deposition, and accelerates the healing process [63].

The first clinical application of platelet-rich preparation was carried out in chronic leg ulcers and a stimulation in the formation of vascularised connective tissue was observed [69].

The main use of PRP in human clinical trials is related to chronic conditions, such as diabetic ulcers, in which the healing is impaired and are characterized by persistent inflammation due to an imbalance between pro-inflammatory and anti-inflammatory cytokines and low growth factor concentration or even due to excess reactive oxygen species [61]. In this sense, growth factors and cytokines play a crucial role in controlling oxidative damage [70]. The regenerative capacity of GFs in PRP

helps shorten the recovery time for wounds and various tissue injuries in mammals [48]. In line with the aforementioned statement, Babaei *et al*. observed the formation of healthy granulation tissue and early complete closure of every wound in 150 patients with diabetic foot ulcers after topical application of PRP [71]. Non-healing ulcers of different etiologies were treated with subcutaneous autologous PRP injections together with topical application of PRP gel and demostrated the potential safety and efficacy of autologous PRP for chronic non-healing ulcers, appreciating a significant reduction in wound size in all treated patients with no side-effects, and additionally a reduction in pain and inflammation in the site of injury thanks to the supression of cytokine release. Similar positive results were obtained in secondary wounds to necrotizing soft tissue infections after topical use of autologous PRP [72], and even in AIDS patients with chronic crural ulcers where enhanced neovascularization and reepithelialization has appreciated [73]. Furthermore, a study carried out by Man *et al*. [72] suggested quantitative improvements of human skin wound healing after topically treating cutaneous flaps with autologous PRP. As shown, several studies have been conducted in human medicine for the treatment of chronic wounds, showing some degree of improvement, reflected by reduction of wound area, volumen, and wound closure [75-77]. Using *in vitro* experimental approaches, Roubelakis *et al*. [35] studied the effect of PRP on the proliferation and migration properties of mesenchymal stem cells (MSC) and skin fibroblasts demonstrating a significant induction of the migration ability and proliferation rate of MSC and fibroblasts. In addition they also showed accelerated healing of ulcers after treatment with PRP dressings and faster neovascularisation of the affected area in real clinical patients. Results which were also obtained by other researchers in randomized, prospective, and retrospective studies. Thus, the use of platelets seems to achieve a faster healing compared to traditional methods [78, 79]. A meta-analysis on the use of PRP in cutaneous wounds compared to control wound therapy, showed that PRP enhanced the wound healing process and ulcers improved significantly in small-hard-to-heal acute and chronic wounds and additionally PRP exert antimicrobial activity against Staphylococcus aureus and Escherichia coli [80]. Moreover, there are also few studies that have assessed the clinical benefit of PRP in skin ageing showing a bioregenerative action, by stimulating fibroblast proliferation, increasing anti-inflammatory factors, angiogeneic factors and proteins related to extracellular matrix remodeling [81]. In a study where patients were treated with ablative fractional carbon dioxide laser, the use of PRP showed reduced erythema and acceleration of the healing process [82]. The use of PRP can also be considered as an effective procedure for facial skin rejuvenation, showing in a clinical study an improvement in general appearance, skin firmness-sagging, and wrinkle state [83]. In addition, the role of PRP in promoting hair survival has also been demonstrated [84].

The curative properties of PRP rely on the fact that platelets in physiological conditions contain a wide variety of growth factors with a crucial healing function, that play an important role in tissue regeneration [58]. The use of PRP in animal models remain the gold-standard for testing novel regenerative therapies and these are useful for subsequent clinical application in both veterinary and human medicine. There are a number of *in vivo* studies in dogs and horses regarding the use of PRP in cutaneous wound therapy. Farghali *et al*. [85] tested the effect of perilesional subcutaneous autologous PRP infiltration in full-thickness cutaneous wounds in dogs. Regarding their clinical evaluation significant increased wound contraction and re-epithelization rate percentages were found. Moreover, a higher collagen deposition, acceleration of granulation tissue maturation, and a reduced scar formation thanks to well-organized collagen fibres was noticeable compared to control wounds. PRP stimulates type I collagen, matrix metalloproteinase I, and increases regulators of cell cycle progression to accelerate wound healing [86]. An enhanced organization of dermal collagen in PRP-treated wounds could be due to an increase in gelatinase B (MMP-9) as it seems to be crucial for the assembly of collagen fibre. In agreement with the aforementioned study, a more rapid epithelial differentiation and enhanced organization of dermal collagen was appreciated in two other clinical studies in equine wounds [87]. Futhermore, a recent study carried out once more in dogs studied the efficacy of intralesional injection of PRP to acute cutaneous wounds. PRP-treated wounds showed both macroscopically and microscopically faster healing than control groups, with angiogenesis and upper granulation formation enhancment at day 7, in addition to a higher collagen deposition, accelerated re-epithelialization and epithelial differentiation. On the other hand, Kim *et al*. [88] studied the curative effect of autologous PRP with very positive results on a large skin defect in a dog.

Second intention skin healing happens when wound edges cannot be approximated as a result of several host factors such as poor blood supply, defect size, presence of infection, systemic diseases, within others, resulting in impaired wound healing [89]. A potent granulation tissue formation promoted by angiogenesis and collagen production by fibroblasts, epithelialization, and contraction is needed for closure of second intention skin defects [90]. With this purpose, Karayannopoulou *et al*. [91] evaluated the use of intralesional PRP on second intention wound healing of acute full-thickness skin defects in dogs and highlighted a significant increase in tissue perfusion which helps the formation of granulation tissue and wound healing by the attraction of nutrients and oxygen to the wounded area, a better collagen architecture in PRP-treated wounds was also shown. The use of locally-injected PRP in survival of skin flaps in dogs was evaluated in a research study carried out by the same authors mentioned in the previous study [92]. In both human and veterinary medicine, one of the major complications regarding skin flaps is necrosis at their distal part, mainly due to insufficient vascularity and blood supply [93]. Results from the present study showed that flap survival was significantly improved in PRP-treated flaps compared to control ones and a decreased oedema was also appreciated. PRP also improved the survival of ischemic random skin flaps in rats [94, 95].

It has been suggested that PRP plays a pivotal role in tissue expansion and skin proliferation [96], enhancing cell proliferation, collagen synthesis, and neovascularization. The combined use of PRP with other treatments to offer better results has also been reported. In line with this, Lian *et al*. [97] showed a synergistic effect when PRP was associated with bone marrow-derived mesenchymal stem cells (BMSCs). In the same way, Park *et al*. [98] described an improved wound healing in PRP + hydrogel treated wounds in mouse compared to control and individually-treated wounds, resulting in a significant shortening of the healing period and enhanced angiogenesis. Manuka honey (MH) is also known due to its inherent wound healing capacity, an *in vitro* study was designed to determine the response of fibroblasts, endothelial cells and macrophages when subjected to culture media supplemented with MH, PRGF, or a combination of both [99], a higher increase in cellular activity was demonstrated in the presence of PRGF + MH, with fibroblasts being the most positively-responsive cells.

Conclusion

Regenerative therapies are, nowadays, the gold-standard for accelerating wound healing in both humans and different animal species as low or non-invasive procedures are prefered. The authors opinion reveal that PRP could be a safe and cost-effective treatment for cutaneous wound healing process managing to shorten the recovery period and therefore improving life quality of our patients.

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