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Platelet-rich plasma - a revolutionary therapeutic option in multi-disciplinary indications

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Abstract:

Background: Platelet-rich plasma (PRP) was originally described as a small volume of plasma that contains higher concentrations of platelets, compared to peripheral blood.

Although currently the use of PRP in most indications is off-label, it is not prohibited. Initially, PRP was used for wound healing and tissue regeneration in fields such as orthopaedics, dermatology, maxillofacial surgery and dentistry.

Aim of the study: The aim of this article was to present and summarise the modern production methods, the mechanism of action at the molecular and biochemical level and the most important uses and indications of PRP in present-day medicine.

Material and methods: A cross-sectional search of relevant literature was performed in databases using accepted wording. Publications from 2003-2023 were included. The entire process has been supplemented with additional procedures to increase the reliability of this publication.

Results: Orthopaedics has gained many minimally invasive therapeutic solutions thanks to PRP. Its effects on ligament and tendon tissues have been studied, where promising data have been proven. Also in aesthetic medicine and dermatology, many treatment strategies have been developed using PRP, mainly for the treatment of acne, androgenic alopecia and delaying tissue ageing as much as possible.

Conclusion: Platelet-rich plasma has found application in the treatment of many conditions in orthopaedics, dermatology, aesthetic medicine and dentistry. It is characterised by good therapeutic efficacy, with relatively low risk. However, high-quality studies are still lacking to provide more reliable data.

Keywords: Platelet-Rich Plasma; Orthopedics; Dermatology; Dentistry

Introduction

Since the 1950s, the first publications were written describing platelet-rich plasma (PRP) as a small volume of plasma containing higher concentrations of platelets than those found in peripheral blood [1]. It was initially used as a transfusion product for the treatment of thrombocytopenia [2]. All other potential uses of PRP for treatment are 'off-label', with this practice not prohibited by the Food and Drug Administration (FDA) if used by a physician with the intention of acting for the benefit of the patient [3]. As an additional treatment

modality, it can improve patients' quality of life and reduce the healthcare burden associated with the treatment of many diseases.

Since the 1990s PRP has begun to be used for wound treatment and tissue regeneration in many fields such as orthopaedics, dermatology, wound care surgery, maxillofacial surgery and dentistry. More recently, plastic surgeons and aesthetic physicians have shown increasing interest in the use of PRP in practice [4].
The aim of this work is to present and summarise the contemporary production methods, the mechanism of action at the molecular and biochemical level and the most important uses and indications of PRP in present-day medicine.

Material and methods

Initially, a cross-sectional search was performed in PubMed database. For this purpose, the following formulations were used: ((Platelet-rich plasma[Title/Abstract]) OR (PRP [Title/Abstract]). Publications from 2003-2023 were included. A complementary hand search of the literature cited in the preselected articles was also performed to find additional publications meeting the objectives of this review. Reviewers conducted an initial qualification of articles based on titles and abstracts to assess their suitability to meet all the objectives of this work. Those that clearly did not meet the inclusion criteria were excluded. The remaining publications were meticulously analysed in full text for final qualification for inclusion in the literature items of this work.

Receiving and mechanism of action

Platelet-rich plasma generally contains 2-9 times more platelets (PLTs) per unit volume than normal blood. According to some studies, PRPs characterised by lower PLT concentrations than those mentioned above do not show an accelerated wound healing effect [5]. To date, there are no specific guidelines for the preparation of PRP in terms of component concentrations. Thus, different commercial kits and uptake protocols exist, resulting in many final products having unique compositions. Differences exist in platelet capture efficiency, isolation method, centrifugation speed. The preparation process begins with collecting blood

from the patient and mixing it with the appropriate anticoagulant. This is followed by centrifugation, during which the red blood cells (RBCs) are separated from the platelet-poor plasma and the 'buffy coat' in which leukocytes and platelets are suspended.

Platelets can be isolated by various methods and administered to the patient as inactivated or by adding calcium chloride or thrombin. They are activated, resulting in the degranulation of their granules and the release of growth factors [6]. They are thought to regulate the secretion of biological factors and stimulate proliferation and differentiation of many cell types. PRP enhances collagen regeneration, triggers angiogenesis, reduces pigment secretion and thus promotes tissue rejuvenation [7].

Regardless of the platelet concentration of PRP, the concentration of growth factors and biologically active proteins in each patient will vary. This is because each organism's response is different and biochemical processes occur in different directions and at different intensities.

Orthopaedics

There are a number of in vitro studies in which the results obtained allow conclusions to be drawn about the effect of PRP on ligament tissue. Fallouh et al. conducted a study for which they used anterior cruciate knee ligament (ACL) remnants as test material. They cultured cells on matrices containing different concentrations of PRP (5%, 10%) and a control group with a concentration of 0%. On the fourth day of the experiment, the group in which the matrix was 10% PRP had a higher cell viability than the others. After one week, the cells in the PRP media produced more collagen and presented overexpression of the COL3 gene. Interestingly, COL1 gene expression and COL/mcg DNA were at similar levels in all study groups [8]. In two-day cultures of human ACL cells, Dhillon et al. showed that cells expressing 5% PRP and 10% PRP showed increased viability and proliferation compared to control medium. In contrast, the incidence of apoptosis was the same in all study groups [9]. In one study by Krismer et al. , the effect of PRP on different leukocyte concentrations on human ACL fibroblasts was investigated. Over 21 days of culture, they found that, irrespective of the presence of leukocytes, cell proliferation was noticeably higher in samples with PRP, but in contrast to the above results, intracellular matrix production was at comparable levels. When considering the metabolism of fibroblasts under the influence of PRP, the expression of genes

responsible for anabolic and catabolic activity was examined. Increased concentrations of COL1A2 and COL2A1 were observed, while reduced COL3A1. In addition, tenascin C (TNC), tenomodulin (TNMD) and aggrecan were also found to be at elevated levels [10]. MMP3 gene expression was also compared in the group that received leukocyte-rich plasma (LR-PRP) to those that were leukocyte-poor (LP-PRP) and those with no PRP at all. The results yielded data that indicated that only the levels of MMP13 AND MMP3 differed and reached statistical significance. Anitua et al. published the results of their study on periodontal cells and related their subject to the effect of PRP on them. They reported that the environment with PRP was characterised by greater cell proliferation, migration and adhesion to type I collagen. They also compared the synthesis of some biomolecules and extracellular matrix components. They found that the presence of PRP had an effect on increasing the levels of VEGF, TSP-1, HGF, CTGF and type I procollagen. In contrast, the production of 2 integrin was lower compared to control samples [11].

Regarding the effect of PRP on tendon tissue structure, one study in which Cross et al. collected supraspinatus muscle tendon samples from patients undergoing reverse shoulder arthroplasty for rotator cuff arthropathy. These samples were divided into two groups according to the severity of degeneration considered histologically. They were cultured in environments with platelet-poor PRP (LP-PRP) and platelet-rich PRP (LR-PRP). In the group where the severity of tendinopathy was at a moderate level, samples in PRP medium showed an elevated COL1A1: COL3A1 ratio. For severe degeneration, we found that the expression of MMP9 AND IL-1 was higher with PRP. In contrast, there was no effect of PRP on COMP and MMP13 expression [12]. In contrast, Zhang et al. cultured human patellar tendon cells for 5 days, where the effects of PRP-activated proteinase-activated receptor 1 (PAR1) and PRP-activated proteinase-activated receptor 4 (PAR4) on tenocyte proliferation and cellular collagen production were studied. In their study, they demonstrated that the presence of PRP increased population doubling time and type I collagen production. Furthermore, the cells were characterised by a more elongated shape compared to the control group. PAR1-PRP and PAR4-PRP stimulated the differentiation of tendon stem cells into their tenocyte-like counterparts, which over time adopted a vascular-like pattern in appearance [13].

Despite the fact that there is still a lack of reliable clinical trials for certain indications in orthopaedic surgery, the popularity of PRP use is steadily increasing. There are many meta-analyses in the literature that provide conflicting data. Some show that the application of PRP

to the site of injury does not provide significant benefits, while many other papers prove the opposite, especially with an emphasis on significant pain reduction and accelerated recovery [14].

Dermatology and aesthetic medicine

Over the past decade, platelet-rich plasma has revolutionised the therapeutic options in dermatology and aesthetic medicine. The main conditions in which PRP has recorded the most spectacular results are mainly acne, scars, melasma, burns and androgenic alopecia [15]. The aetiology of acne is complex and depends on many factors. It most commonly appears during adolescence and the magnitude of the prevalence is shown by the percentage of the global population that is 9.4% [16]. An inherent pathophysiological phenomenon in the aetiology of acne lesions is the proliferation of Propionibacterium bacteria and their induction of pathology at the level of the hair and sebaceous follicles. The clinical picture of acne usually shows papules, pustules, comedones, nodules, abscesses and scars, which sometimes follow the above-described lesions [17]. Atrophic scars are the most challenging to treat, due to their permanent destruction by the chronic inflammatory process. They often pose a psychological problem for patients [18]. The most commonly used treatments for acne are retinoids and topical antibiotics. Unfortunately, they have limited efficacy and are associated with a wide spectrum of side effects, such as skin irritation and dryness or their phototoxicity [19]. All these facts were the reason for the search for new, less invasive therapeutic solutions. A number of studies have emerged that have shown that PRP presents very good results in the treatment of acne scars [20]. On the other hand, in vitro studies have shown that PRP has the ability to inhibit the growth of Propionibacterium [21]. Gomez et al. in their study showed a significant reduction in both inflammatory lesions and acne scars [22].
Interesting findings were also noted by Abdel et al. who observed that the use of PRP increased the efficacy of subsequent CO_2 laser therapy in the treatment of acne scars [20].

Another condition that has become a large-scale indication for treatment with PRP is androgenetic alopecia. The main manifestation of this condition is progressive hair loss. There are two types of alopecia, those that will leave scars and those that are devoid of this process. The latter are associated with a better prognosis and greater therapeutic options. Androgenetic alopecia affects both sexes, which translates into a relatively high prevalence. The biggest

factor that influences the prevalence of this disease is genetic predisposition. Undoubtedly, the manifestation of these symptoms causes self-esteem problems. Current treatment of androgenetic alopecia is limited to two drugs - minoxidil and finasteride. Minoxidil, which is used topically, dilates the blood vessels, thereby prolonging the anagen phase of the hair and increasing the size of the hair follicles. This is related to the release and action of prostaglandins. The second drug is oral finasteride, which blocks 5-reductase, whose activity is greater in men. In the search for a new treatment strategy for androgenic alopecia, PRP has emerged as a solution with high efficacy. Khatu et al. demonstrated that the application of PRP resulted in the appearance of new hair, root resilience and thus a reduction in hair loss and an increase in hair thickness [23]. Furthermore, the efficacy of PRP has also been confirmed for the treatment of alopecia aerate. As Singh et al. demonstrated, PRP therapy was followed by a significant improvement [24]. The mechanism of action of PRP in the treatment of alopecia is still not fully understood, thus raising many questions for researchers. The function of certain growth factors, such as fibroblastic growth factor (FGF), which stimulates the proliferation of papilla cells, leading to an increase in hair length, has been described. The effects of PDGF and VEGF, which presumably act in the follicle bulb to bind to relevant stem cell receptors to activate hair growth, have also been investigated [25].

The topic of greatest interest to the general population is skin ageing, commonly defined as a progressive loss of skin homeostasis. It is a complex process as a result of many processes such as UV radiation or chemical exposure. Intrinsic factors such as hormonal regulation or inflammatory processes are also important and cause multidimensional changes in the body. Various studies have shown that PRP restores vitality to ageing skin, restores elasticity and increases the amount of collagen in the skin, improves blood flow in the skin's vessels and improves smoothness and tone [26].

Wound surgery

Platelet-rich plasma is recognised as a safe and effective method that has a positive impact on the wound healing process. PRP is becoming an increasingly used tool that can improve patients' quality of life and reduce the burden of healthcare. One of the most common public health problems is diabetes. Fifteen per cent of patients with this disease develop a diabetic foot, which is a significant factor in the amputation of the affected limb [27]. Due to the

activation of platelets encapsulated in PRP and the release of various cytokines and growth factors from their granules, the use of PRP in assisted therapy for the treatment of ulcers is being investigated. Some studies have shown that in patients treated with PRP, a reduction in wound extensiveness was observed, thus providing evidence for the implementation of PRP therapy in the treatment of ulcers [28]. One study looked at the interaction of PRP and hyaluronic acid and their effect on wound regeneration on the lower limb. It proved that re-epithelialisation time was shorter for the combination therapy than for hyaluronic acid-only therapy. This demonstrates that technology using PRP can find application in the treatment of soft as well as hard wounds [29].

In addition, PRP increases the survival of transplanted fat, shedding new light on its potential use in plastic and reconstructive surgery [30]. In fat transplantation containing adipose tissue-derived mesenchymal stem cells, where simultaneously attached to PRP therapy, better results were observed in terms of facial rejuvenation, facial scarring and soft tissue loss [31]. Setta et al. conducted a randomised trial involving 21 patients with ulcers. Patients were randomly assigned to be treated twice a week with an autologous gel containing PRP. They found that patients who received PRP had a shorter mean healing time than those who did not receive such treatment (11.5 weeks vs. 17 weeks) [32].

Lil et al. in their study showed that PRP application was able to reduce the wound area by 80% more than in the control group [33]. In contrast, Ahmed et al. compared the efficacy of PRP gel with antiseptic iodine ointment. They found that PRP therapy resulted in a higher healing rate at 2 weeks (P=0.003) and at 4 weeks (P=0.044) than iodine ointment. In contrast, the difference in healing slowed at week 8 of therapy, which may be explained by down-regulation of receptors by continuously elevated concentrations of growth factors [34].

A study that evaluated the efficacy of PRP in wound healing in terms of wound area reduction was an experiment by Mohammadi et al. who reported an efficacy of 51.9 % reduction compared to no PRP supplementation [35]. The efficacy of the therapy has also been demonstrated in the treatment of pressure sores, where the effects were explained by increased local platelet concentrations and sustained induction of myofibroblasts [36].

Maxillo-facial surgery and dentistry

Professions in which PRP has found widespread use include maxillo-facial surgery and dentistry. One of the applications of PRP therapy is the regeneration of bone and connective tissue in the maxillo-facial area. High concentrations of platelets are responsible for the regenerative processes. Currently, PRP is used to improve structural integrity and as a scaffold for tissue growth by causing stem cell migration. The properties of PRP have found application in accelerating alveolar healing after extractions and in implantology, where bone defects around the implant are treated [37].

Beneficial effects of PRP have been found in patients who have used autologous bone grafts for jawbone or sinus reconstruction. Robiony et al. in their study to evaluate a new method of restoring severe mandibular atrophy using platelet-rich plasma during distraction osteogenesis, demonstrated the efficacy of PRP in achieving a faster implant [38]. In contrast, Simonpieri et al. in their study compared bone graft density at 3 and 6 months after maxillary sinus bone reconstruction. At 6 months after surgery, they found that the group that received additional PRP had a higher graft density, compared to the control group [39].

Conclusions

Although platelet-rich plasma has found its way into the treatment of many conditions in the fields of orthopaedics, dermatology, aesthetic medicine, maxillofacial surgery and dentistry, there is still a lack of high-quality studies on larger numbers of patients to provide more reliable and valid data. Nevertheless, platelet-rich plasma has been changing people's lives for years by helping them to get rid of their conditions. It is characterised by good therapeutic efficacy, with a relatively low risk of serious side effects, which should also be taken into account when deciding on a treatment strategy.

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Conceptualization, Aleksandra Kiełkowicz and Piotr Pisera; methodology, Daniel Ślusarczyk and Bartłomiej Żmuda; software, Filip Pactwa and Zuzanna Popińska; check, Wiktoria Jakubowska and Michał Żuberek; formal analysis, Aleksandra Kiełkowicz and Daniel

Ślusarczyk; investigation, Piotr Pisera and Zuzanna Popińska; resources, Bartłomiej Żmuda, Wiktoria Jakubowska and Michał Żuberek; data curation, Filip Pactwa, Daniel Ślusarczyk and Wiktoria Jakubowska; writing - rough preparation, Aleksandra Kiełkowicz; writing - review and editing, Aleksandra Kiełkowicz and Piotr Pisera; visualization, Aleksandra Kiełkowicz, Bartłomiej Żmuda and Michał Żuberek; supervision, Filip Pactwa and Zuzanna Popińska; project administration, Aleksandra Kiełkowicz.
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