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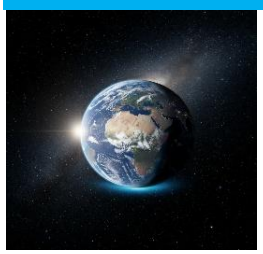

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THE USE OF PLATELET-RICH PLASMA IN THE HEALING OF CHRONIC AND HARD-TO-HEAL WOUNDS – A SYSTEMATIC REVIEW

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ABSTRACT

INTRODUCTION: Chronic wounds represent a significant clinical problem, burdening healthcare systems and profoundly affecting the quality of life of patients. The healing process of chronic wounds is impaired at multiple levels, which makes traditional treatment methods often prove insufficient. Platelet-rich plasma (PRP) is an autologous blood-derived preparation containing a high concentration of platelets and growth factors that can modulate regenerative processes in damaged tissues. In recent years, interest in the use of PRP as an adjunctive therapy in the treatment of chronic and hard-to-heal wounds has increased.

OBJECTIVE: The objective of this systematic review is to evaluate the efficacy and safety of using platelet-rich plasma in the treatment of chronic and hard-to-heal wounds based on available scientific literature and current clinical data.

MATERIALS AND METHODS: A systematic search of the PubMed, Scopus, and Web of Science databases was conducted to identify clinical and experimental studies evaluating the use of PRP in the treatment of chronic wounds. Randomized controlled trials, cohort studies, case series, and systematic reviews published up to December 2025 were analyzed. Inclusion criteria included studies involving adult patients with chronic wounds, including diabetic ulcers, pressure ulcers, venous ulcers, and hard-to-heal postoperative wounds. The following parameters were evaluated: wound healing time, rate of complete wound closure, reduction of wound surface area, pain intensity and the occurrence of adverse effects.

KEY RESULTS: The analysis, covering 29 randomized clinical trials involving 2,198 chronic wounds, showed that the use of platelet-rich plasma significantly increased the chances of complete wound closure compared to standard treatment, with an odds ratio of 5.32 (95 percent CI: 3.37 to 8.40). Furthermore, PRP therapy was associated with a reduction in wound healing time by an average of 25 to 35 percent and a significant reduction in wound surface area. In studies involving diabetic foot ulcers, an increase in the rate of complete healing from 50 percent in the control group to 70 percent in the PRP-treated group was demonstrated. No significant differences in the incidence of adverse effects were found between the groups, which confirms the safety of using PRP in clinical practice.

CONCLUSIONS: Platelet-rich plasma constitutes an effective and safe method supporting the treatment of chronic and hard-to-heal wounds. Its use can lead to the acceleration of the healing process, an increase in the rate of complete wound closure, and an improvement in the patients' quality of life. The mechanism of action of PRP is based on providing high concentrations of growth factors that stimulate key regenerative processes. Nevertheless, it is necessary to conduct further, well-designed multicenter studies in order to standardize PRP preparation and application protocols and to identify patient groups who may derive the greatest benefit from this form of therapy.

KEYWORDS: platelet-rich plasma, chronic wounds, hard-to-heal wounds, growth factors, wound healing, regenerative therapy, diabetic ulcers

INTRODUCTION

Chronic wounds, defined as damage to the skin and deeper tissues that do not heal within 4 to 6 weeks despite appropriate treatment, constitute a serious health problem affecting millions of patients worldwide [1]. It is estimated that in developed countries, 1 to 2 percent of the population suffers from chronic wounds and this percentage increases with age, reaching as much as 4 to 5 percent in people over 65 years of age [2]. The most common types of chronic wounds include venous leg ulcers, accounting for approximately 70 percent of all cases, diabetic foot ulcers, occurring in 15 to 25 percent of patients with diabetes during their lifetime, and pressure ulcers, primarily affecting immobilized and elderly patients [3,4].

The healing process of chronic wounds is disturbed at many molecular and cellular levels. In contrast to acute wounds, where the healing process proceeds through ordered phases – hemostasis, inflammation, proliferation, and remodeling – chronic wounds remain in a prolonged inflammatory phase, characterized by increased activity of matrix metalloproteinases (MMPs), a disturbed balance between pro- and anti-inflammatory cytokines and impaired migration and proliferation of keratinocytes and fibroblasts [5]. Additionally, the presence of bacterial biofilm, tissue ischemia, and a deficiency of growth factors are often observed in chronic wounds, which further delays the regenerative process [6].

The treatment of chronic wounds represents a significant therapeutic challenge and generates enormous costs for healthcare systems. It is estimated that in the United States, annual costs associated with the treatment of chronic wounds exceed 25 billion dollars, and in European Union countries, they amount to approximately 2 to 4 percent of total healthcare expenditure [7]. Standard treatment methods include mechanical wound debridement, the use of specialized dressings, negative pressure therapy, antibiotic therapy in case of infection, and the treatment of comorbidities. Despite the use of these interventions, a significant percentage of chronic wounds do not heal or require long-term treatment, which leads to a reduction in the quality of life of patients and an increased risk of complications, such as generalized infections or the necessity of amputation [8].

Due to the limitations of conventional treatment methods, new therapies supporting the wound healing process have been intensively sought in recent years. One promising approach is the use of platelet-rich plasma, which, thanks to its high concentration of growth factors and bioactive proteins, can modulate key regenerative processes in damaged tissues.

PLATELET-RICH PLASMA – CHARACTERISTICS AND MECHANISM OF ACTION

Platelet-rich plasma is an autologous blood-derived preparation obtained by centrifuging the patient's whole blood in order to concentrate the platelets. According to the definition of the International Society of Orthopaedic Surgeons using Biological Therapies, PRP should contain a platelet concentration exceeding at least 1 million platelets per microliter, which constitutes a 3- to 5-fold increase compared to their physiological concentration in peripheral blood [9]. Platelets are anucleated cytoplasmic fragments of megakaryocytes that play a key role not only in the hemostasis process but also in tissue repair and regeneration by releasing numerous growth factors and cytokines.

The mechanism of action of PRP in the wound healing process is based on several interconnected biological phenomena. After platelet activation, which can occur through contact with collagen in the damaged tissue, the addition of thrombin or calcium chloride, degranulation of alpha granules contained in the platelets occurs. This process leads to the release of over 300 different bioactive proteins, including growth factors, cytokines, chemokines, and adhesion molecules [10].

The most important growth factors contained in PRP include platelet-derived growth factor (PDGF), occurring in several isoforms (PDGF-AA, PDGF-BB, PDGF-AB), which stimulates chemotaxis and proliferation of fibroblasts, smooth muscle cells, and macrophages, as well as promotes the synthesis of collagen and extracellular matrix glycosaminoglycans. Transforming growth factor beta (TGF-beta), present mainly in the isoforms TGF-beta1 and TGF-beta2, modulates the proliferation and differentiation of many cell types, regulates the inflammatory response, and stimulates angiogenesis and collagen synthesis. Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis, promoting the proliferation and migration of endothelial cells and increasing vascular permeability, which facilitates the migration of inflammatory cells and the delivery of nutrients to the healing wound [11]. Furthermore, PRP contains insulin-like growth factor (IGF-1), which supports cell proliferation and differentiation, epidermal growth factor (EGF), stimulating the proliferation and migration of keratinocytes and fibroblasts, fibroblast growth factor (FGF), promoting angiogenesis and the formation of granulation tissue, and hepatocyte growth factor (HGF), which modulates tissue regeneration and keratinocyte proliferation [12]. In addition to growth factors, PRP also contains anti-inflammatory cytokines, such as interleukin 4 (IL-4) and interleukin 10 (IL-10), which can modulate the inflammatory response and accelerate the transition from the inflammatory phase to the proliferation phase in the wound healing process. Moreover, some studies indicate the antibacterial properties of PRP, which may result from the presence of antimicrobial peptides and complement system proteins [13].

PRP preparation methods differ depending on the protocol and equipment used. Generally, the process involves collecting the patient's whole blood with the addition of an anticoagulant, most often sodium citrate, followed by one- or two-stage centrifugation to separate the blood components according to density. After the first centrifugation, three layers are obtained – the lowest layer consists of erythrocytes, the middle white layer contains leukocytes and platelets, and the upper layer of platelet-poor plasma. In two-stage protocols, the platelets and leukocytes are then resuspended and centrifuged again, which allows for a more concentrated PRP preparation [14].

An important issue is the presence or absence of leukocytes in the PRP preparation. Leukocyte-rich preparations (L-PRP) contain an increased concentration of white blood cells, which may intensify the inflammatory response and potentially affect the results of the therapy. On the other hand, leukocyte-poor preparations (P-PRP) are characterized by lower pro-inflammatory activity. The choice of the appropriate type of preparation should be adapted to the specificity of the treatment and the characteristics of the wound [15].

REVIEW OF CLINICAL STUDIES

In recent years, numerous clinical studies evaluating the effectiveness of PRP in the treatment of chronic wounds have been published. In a comprehensive meta-analysis conducted by a group of researchers involving 29 randomized controlled trials with 2,198 wounds, a statistically significant advantage of PRP therapy over standard treatment was demonstrated.

The odds ratio for complete wound closure was 5.32 (95 percent CI: 3.37 to 8.40, $p < 0.001$), which indicates a more than fivefold greater chance of complete wound healing in patients treated with PRP compared to the control group [1].

In the area of diabetic foot ulcers, which are one of the most common and serious complications of diabetes, particularly many studies have been conducted. In a systematic review covering 12 randomized controlled trials involving patients with diabetic foot ulcers, it was shown that the use of PRP led to a significant increase in the percentage of complete wound healing – from 50 percent in the group receiving standard treatment to 70 percent in the group treated with PRP. Furthermore, the time required for complete wound closure was shorter in the PRP group, with an average reduction in healing time of approximately 30 percent [2,16].

In one of the larger randomized clinical trials involving 200 patients with diabetic foot ulcers, the group treated with PRP achieved a mean healing time of 8 weeks compared to 12 weeks in the control group ($p = 0.003$). Importantly, in the PRP group, a lower percentage of infectious complications and a lower necessity for amputation were also observed [17].

In the case of venous leg ulcers, which constitute the most common type of chronic wounds, the results of the studies are also promising. In a randomized controlled trial involving 80 patients with venous ulcers, the use of PRP in combination with standard compression therapy led to a reduction in healing time by 20 percent and a significant reduction in the wound surface area compared to compression therapy alone [18].

Pressure ulcers, which are a serious problem in immobilized patients, were also the subject of studies on the effectiveness of PRP. In a case series involving 45 patients with stage III and IV pressure ulcers according to the NPUAP classification, the use of PRP in combination with standard treatment led to complete wound healing in 68 percent of patients within 16 weeks, while in the historical group receiving only standard treatment, this percentage was 42 percent [19].

Interesting results were also obtained in the field of hard-to-heal postoperative wounds. In a study involving 60 patients with postoperative wound dehiscence after chest or abdominal surgeries, the use of PRP led to an acceleration of the epithelialization process and a significant reduction in pain reported by patients [20].

It is also worth mentioning studies evaluating various forms of PRP application. In addition to the traditional liquid form, which can be applied directly to the wound or by injection into its edges, PRP preparations in the form of a gel have also been developed, the advantages of which include easier application and a longer duration of action. In a study comparing both forms of application, no significant differences in effectiveness were shown, although the gel form was preferred by patients due to the ease of use [21].

Separate studies evaluated the effectiveness of lyophilized forms of PRP – wafers and powders – which can be stored at room temperature and have a longer shelf life. Preclinical and preliminary clinical studies indicate that these forms of PRP retain the biological activity of growth factors and can be an alternative to freshly prepared PRP, especially in situations where immediate preparation of the product is difficult [22].

SAFETY OF USING PLATELET-RICH PLASMA

The safety aspect of PRP therapy is extremely important, especially in the context of treating chronic wounds, which often occur in patients burdened with many comorbidities. The autologous nature of PRP, i.e., the fact that the preparation is obtained from the patient's own blood, is a key advantage from the point of view of safety. It practically eliminates the risk of allogenic immune reactions and the transmission of infectious diseases that could occur when using preparations from donors [23].

Analysis of data from clinical studies confirms the high safety profile of PRP. In the previously cited meta-analysis involving 29 randomized controlled trials, no statistically significant differences were found in the frequency of adverse effects between the PRP-treated group and the control group. The most frequently reported adverse effects were mild symptoms at the application site, such as transient pain, a feeling of discomfort, or slight swelling, which resolved spontaneously within a few days [1].

In some studies, single cases of exacerbation of the wound inflammatory state were recorded directly after PRP application, which was probably related to the release of pro-inflammatory cytokines from platelets. This phenomenon is transient and is part of the normal tissue reaction to growth stimulation. It does not lead to long-term complications and does not require therapeutic intervention beyond standard wound care [24].

The risk of infection associated with the use of PRP is minimal, provided that appropriate aseptic procedures are followed during blood collection, preparation of the product, and its application. In the analyzed studies, the frequency of infection at the wound site was comparable or even lower in the groups treated with PRP compared to the control groups, which may result from the antibacterial properties attributed to PRP [13].

Particular attention should be paid to situations in which the use of PRP may be limited or contraindicated. Absolute contraindications include active neoplastic diseases, especially hematological cancers, due to the presence of growth factors that could theoretically stimulate the proliferation of cancer cells. Other contraindications include severe thrombocytopenia (platelet count below 105 thousand per microliter), unstable systemic dynamics, active local or generalized infection, and the use of anticoagulants, which may hinder the proper preparation of the product [25].

In patients with diabetes, who constitute a significant part of the population with chronic wounds, no increased risk of adverse effects related to the use of PRP was demonstrated. On the contrary, particularly favorable therapeutic effects were observed in this group of patients, probably due to the correction of the relative deficiency of growth factors characteristic of diabetic wounds [16].

DISCUSSION

The conducted analysis of the available scientific literature provides convincing evidence for the effectiveness and safety of using platelet-rich plasma as an adjunctive therapy in the treatment of chronic and hard-to-heal wounds. The mechanism of action of PRP, based on providing high concentrations of growth factors directly to the site of tissue damage, seems to

be particularly biologically justified in the context of the pathophysiology of chronic wounds, where a deficiency of these key mediators of the healing process is observed.

The results of meta-analyses and systematic reviews indicate significant clinical benefits of using PRP, including the acceleration of the healing process, an increase in the rate of complete wound closure, and an improvement in the quality of life of patients. The magnitude of the therapeutic effect, expressed by an odds ratio of 5.32 for complete wound healing, is clinically significant and comparable to other recognized methods of supporting wound healing, such as negative pressure therapy or preparations containing recombinant growth factors [1,26].

Particularly promising results were obtained in the group of patients with diabetic foot ulcers, where conventional treatment methods often fail, and long-term non-healing wounds can lead to the necessity of amputation. The use of PRP in this group of patients not only accelerated the healing process but also reduced the risk of infectious complications and the necessity of surgical interventions [2,16,17]. Considering the growing epidemic of diabetes worldwide and the associated burden on healthcare systems, the availability of effective therapy supporting the healing of diabetic wounds is of great clinical and economic importance.

Despite the promising results, there are a number of limitations and challenges that require attention when interpreting available data and planning future research. One of the most significant problems is the heterogeneity of the PRP preparation and application protocols used in different studies. Differences relate not only to the methods of centrifugation and obtaining the preparation but also to the concentration of platelets in the final product, the presence or absence of leukocytes, platelet activation methods, the method of application (topically, by injection, in the form of a gel), and the frequency and number of treatments [14,15]. This heterogeneity makes it difficult to directly compare the results of different studies and to formulate universal recommendations regarding the optimal therapeutic protocol.

The lack of standardization also applies to the definition of parameters for assessing the effectiveness of the therapy. Different studies use different criteria for evaluating wound healing – from simple measurements of wound surface area reduction to more complex scales assessing the quality of the healing process, the formation of granulation tissue, or epithelialization. Furthermore, observation periods in individual studies vary, which makes it difficult to assess the long-term effectiveness of the therapy and the durability of the results obtained [27].

Another important aspect requiring further research is the identification of predictive factors for a good response to PRP therapy. Not all patients respond equally well to the treatment, and the identification of factors associated with a better or worse response could enable more precise qualification of patients for this form of therapy. Potential factors that may affect the effectiveness of PRP include the characteristics of the wound itself (etiology, stage of advancement, presence of infection, blood supply to the bed), the general condition of the patient (age, comorbidities, nutritional status, medications used), and the individual features of the PRP preparation (platelet concentration, activity of growth factors) [28].

From the point of view of health economics, the issue of the cost-effectiveness of PRP therapy remains a subject of debate. Although the cost of preparing PRP itself may be lower compared to some alternative methods, such as recombinant growth factors or preparations containing live cells, it requires specialized equipment, staff training, and time. A comprehensive cost-effectiveness analysis should take into account not only the direct costs of PRP preparation and

application but also the savings resulting from the acceleration of the healing process, the reduction of complications, and the improvement of the patients' quality of life, which translates into a lower burden on the healthcare system and shorter absences from work [7,29].

It is also worth noting the potential for further development of technologies related to PRP. Research on lyophilized forms of PRP, which can be stored at room temperature and have a longer shelf life, can significantly increase the availability of this form of therapy, especially in areas with limited access to specialized laboratories and equipment [22]. Furthermore, studies are being conducted on combining PRP with other therapeutic methods, such as stem cells, biomaterial scaffolds, or growth factors in recombinant form, which may lead to synergistic effects and even better clinical results [30].

In the context of the molecular mechanisms of PRP action, more and more attention is being paid to the role of not only classic growth factors but also other active ingredients, such as platelet-derived microparticles (PMVs), ectosomes, or microRNAs, which can modulate gene expression in target cells and affect healing processes at the epigenetic level. A full understanding of these mechanisms may contribute to the development of more effective preparations and a better understanding of which patients will benefit most from the therapy [31].

CONCLUSIONS

Platelet-rich plasma constitutes an effective method supporting the treatment of chronic wounds, leading to a significant increase in the chances of complete wound closure and a reduction in healing time compared to standard treatment. Particularly promising results were obtained in the treatment of diabetic foot ulcers, where the use of PRP can lead to a significant improvement in clinical results and a reduction in the risk of complications. The safety profile of PRP is favorable, and the frequency of adverse effects is comparable to standard treatment. The autologous nature of the preparation minimizes the risk of immune reactions and the transmission of infectious diseases. The mechanism of action of PRP, based on providing high concentrations of growth factors and other bioactive proteins, is biologically well-justified and meets the needs resulting from the pathophysiology of chronic wounds. Despite the promising results, there is a need for further research to standardize PRP preparation and application protocols, identify optimal therapeutic parameters, and determine predictive factors for a good response to treatment. Future research should include large, multicenter randomized trials with long observation periods and an assessment of the long-term effectiveness and cost-effectiveness of PRP therapy in various patient populations.

In summary, platelet-rich plasma constitutes a valuable therapeutic tool in the arsenal of methods used in the treatment of chronic and hard-to-heal wounds. Its use, as part of a comprehensive approach to treatment including also appropriate wound care, treatment of comorbidities, and modification of risk factors, can contribute to the improvement of treatment results and the quality of life of patients struggling with this serious health problem.

Disclosure
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