

THE RATIONALE FOR PLATELET-RICH PLASMA (PRP) THERAPY IN CHRONIC WOUNDS : SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Chronic wounds are common and reduce quality of life. The financial burden of dressing materials, amputation costs, and the ongoing and extended need for human resources to treat wounds affects healthcare resource utilization. Platelet-rich plasma (PRP) has been shown to increase the healing rates of open diabetic foot ulcers and venous ulcers.

The aim: This article demonstrated the rationale for platelet-rich plasma (PRP) therapy in chronic wounds.

Methods: This study demonstrated that it met all of the requirements by comparing itself to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. As a result, the specialists were able to ensure that the study was as up to date as possible. Publications published between 2013 and 2023 were considered for this search strategy. This was accomplished using a variety of online reference sources, including Pubmed and SagePub. It was chosen not to include review pieces, previously published works, or works that were just partially completed.

Result: In the PubMed database, the results of our search brought up 76 articles and SagePub 62 articles. The results of the search conducted for the last year of 2013 yielded a total 16 articles for PubMed and 12 articles from SagePub. In the end, we compiled a total of six papers.

Conclusion: PRP is composed of several components obtained from platelets, including growth factors and cytokines. These bioactive substances have a significant role in modulating processes such as inflammation, angiogenesis, stem cell activity, and cellular proliferation.

Keyword: Chronic wounds; Platelet; Platelet rich plasma

INTRODUCTION

Platelet-rich plasma (PRP) is autologous blood with a platelet concentration above the physiological baseline value. PRP is obtained by a centrifugation process which separates the liquid and solid components of blood. PRP injections have received considerable attention as a treatment method for musculoskeletal conditions due to their safety and ability to promote soft tissue healing.¹ Tissue regeneration in musculoskeletal conditions is achieved after percutaneous injection of PRP.² All blood cells originate from common pluripotent stem cells, which differentiate into different cell lines.^{3,4}

Each of these series of cells contains precursors that can divide and mature. Platelets, develop from the bone marrow. Platelets are nucleated, discoid cellular elements of varying sizes and densities about 2 µm in diameter, the smallest density of all blood cells.¹ The physiological number of platelets circulating in the bloodstream ranges from 150,000 to 400,000 platelets per µL.³ The term PRP is used as an autologous blood sample that has a platelet concentration above the normal level contained in blood plasma.⁵

PRP preparation involves drawing autologous whole blood from the patient followed by a 1-2 step centrifugation process to separate the plasma from the red blood cells and leukocytes. Isolation methods include the type of collection tube and centrifuge speed, both of which play a role in the final concentration of platelets and leukocytes in the PRP preparation.⁶ Platelets contain several secretory granules that are important for platelet function. There are 3 types of granules: solid granules, o granules, and lysosomes. In each platelet there are approximately 50-80 granules, the most abundant of the 3 types of granules. Platelets are responsible for the aggregation process.^{4,7}

The main function of platelets is homeostasis through 3 processes: adhesion, activation, and aggregation. During vascular lesions, platelets are activated, and their granules release factors that promote coagulation.³ When activated, platelets secrete a growth factor-filled soup that plays a role in the healing process of wounds. Platelet-rich plasma (PRP), is obtained by centrifuging the patient's venous blood after the platelets have been activated with collagen, calcium chloride, and/or autologous thrombin, and then carefully removing the supernatant, which is known as platelet-poor plasma (PPP).^{6,7}

This is one method for administering activated platelets to wounds. PRP is typically injected into the lesion and/or given topically, and a moisture-retentive dressing is subsequently placed in or over the wound to prevent further loss of moisture. PRP has been delivered at varying times, depths, and frequencies to chronic and acute wounds using a variety of PRP doses and vehicles, with the goal of achieving a wide range of effects.⁵

In other hand, chronic wounds is widely known as a loss of continuity of the skin secondary to injury that persist longer than 6 weeks. It is categorized into three types which is vascular ulcers, diabetic ulcers and pressure ulcers. All of them have same characteristic such as persistent inflammatory phase, impaired proliferation, microbial colonization, and failed completion of four phases of wound healing properly in normal timeframe.²³

PRP has been shown to increase the healing rates of open diabetic foot ulcers and venous ulcers, and it may also lower the incidence of pain and surgical site infection (SSI) in open and closed acute surgical wounds. These findings have been published by meta-analyses.^{5,6,8} Chronic wounds are prevalent ailments that significantly affect the quality of life of individuals. The utilization of healthcare resources is significantly impacted by the substantial financial burden associated with the procurement of dressing materials, expenses related to amputation, and the ongoing and extended requirement for human resources to treat wounds.^{9,10}

This article demonstrated the rationale for platelet-rich plasma (PRP) therapy in chronic wounds.

METHODS

The study's leader made sure that the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 rules were followed to the letter. The goal of this method is to make sure that the investigation's results are correct. The main goal of this study was to look rationale for platelet-rich plasma (PRP) therapy in chronic wounds.. The main goal of this study is to show how important the above-mentioned and book-discussed subjects are. Researchers had to meet certain standards in order to be able to take part in the study.

One of the requirements was that the paper had to be written in English and be mostly rationale for platelet-rich plasma (PRP) therapy in chronic wounds. Both of these conditions must be met for the paper to be released. A number of the articles being looked at came out in 2018—within the time range that was chosen to be relevant to the goals of this systematic review. In an academic setting, you can't send in editorials, submissions without a Digital Object Identifier (DOI), review articles that have already been published, or submissions that are exact copies of journal articles that have already been published.

Pubmed journal database
search results = 76
articles

SagePub database search
results =
62 articles

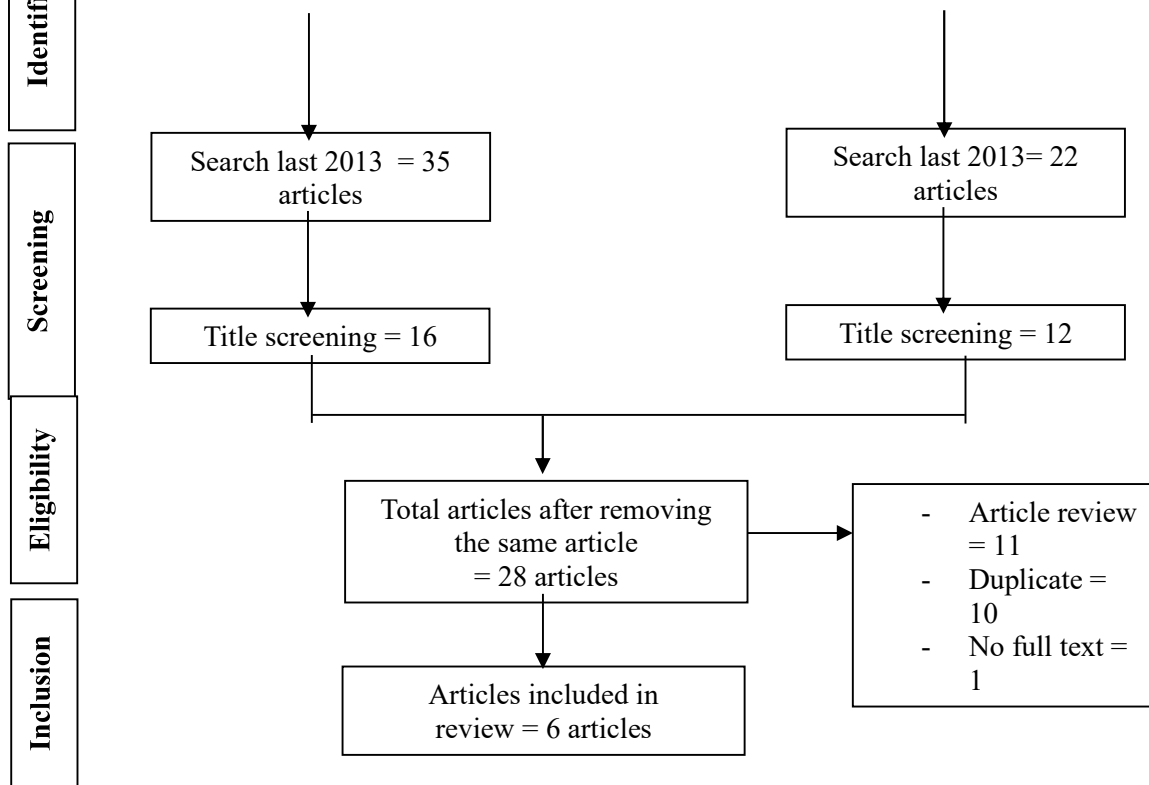


Figure 1. Article search flowchart

We used “platelet rich plasma”; and “chronic wounds” as keywords. The search for studies to be included in the systematic review was carried out from September, 23th 2023 using the PubMed and SagePub databases by inputting the words: (“platelet rich plasma”[MeSH Terms] OR (“platelet rich”[All Fields] AND “plasma”[All Fields]) OR “platelet rich plasma”[All Fields] OR (“platelet”[All Fields] AND “rich”[All Fields] AND “plasma”[All Fields]) OR “platelet rich plasma”[All Fields]) AND (“chronic”[All Fields] OR “chronical”[All Fields] OR “chronically”[All Fields] OR “chronicities”[All Fields] OR “chronicity”[All Fields] OR “chronicization”[All Fields] OR “chronics”[All Fields]) AND (“injuries”[MeSH Subheading] OR “injuries”[All Fields] OR “wounds”[All Fields] OR “wounds and injuries”[MeSH Terms] OR (“wounds”[All Fields] AND “injuries”[All Fields]) OR “wounds and injuries”[All Fields] OR “wound s”[All Fields] OR “wounded”[All Fields] OR “wounding”[All Fields] OR “woundings”[All Fields] OR “wound”[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter])) used in searching the literature.

The researchers made sure that the abstract and title of each study were included. The essayists then picked research from the literature that was relevant. This was found by looking at a lot of studies that all followed the same trend. Before they are sent in, all writing must be in English and have never been published before. The systematic review only looked at studies that met all of the requirements to be included. This makes sure that the search results are only about what the user asked for. We don't pay attention to studies that don't meet our standards. The study results will be carefully looked over.

Everyone who wrote the paper looked at the research in the title and abstract of every paper before choosing which ones to read more deeply. The next step is to choose which articles to include from all the ones that meet the review's requirements. Then we'll choose which stories to include in the review based on what we find. This is how papers that need to be looked at more closely are chosen.

RESULT

In the PubMed database, the results of our search brought up 76 articles and SagePub 62 articles. The results of the search conducted for the last year of 2013 yielded a total 16 articles for PubMed and 12 articles from SagePub. In the end, we compiled a total of six papers.

Table 1. The literature include in this study

Author	Origin	Method	Participant	Wound	Dose	Result
Lin, 2023 ¹¹	China	Randomized Controlled Trial	120 patients	Chronic refractory wounds (lower extremity)	PRF (Platelet-Rich Fibrin) gel for 5-7 days	The utilization of a combination of PRF (Platelet-Rich Fibrin) and silver nanoparticle (AgNP) dressing has demonstrated significant efficacy in mitigating pain and local inflammation in individuals suffering from chronic refractory wounds. Moreover, this treatment approach has been found to enhance the rate of wound healing, expedite the overall healing process, and diminish the likelihood of problems, such as the spread of infection.
Helmy, 2021 ¹²	Egypt	Randomized Controlled Trial	80 patients	Chronic venous leg uclers (lower extremity)	Intradermal and subdermal injection of 2-4 mL PRP weekly, in all edges and in the granular floor of the ulcer for 4-6 sessions	This study provides evidence that PRP is efficacious and statistically significant in enhancing the wound healing process in individuals with chronic leg venous ulcers. The technique of PRP is characterized by its simplicity, safety, and a relatively quick learning curve.
Pires, 2021 ¹³	Brazil	Randomized Controlled Trial	36 patients	Chronic venous leg uclers (lower extremity)	PRP gel for 5-7 days	PRP + petrolatum gauze did not increase bacterial growth or microbial load in chronic venous ulcers when compared to petrolatum gauze alone and could be considered as an advanced treatment for these types of chronic wounds.
Tsai, 2019 ¹⁴	Taiwan	Randomized Controlled Trial	87 patients	Diabetic foot (lower extremity)	Intradermal and subdermal injection of 8 mL PRP weekly, in all edges and in the granular floor of the ulcer for 12 sessions	Compared to conventional advanced wound dressings, the combination of PRP injections and platelet-derived patches substantially improved the healing outcomes of patients with chronic wounds, particularly diabetic patients.
Liao, 2019 ¹⁵	China	Randomized Controlled Trial	60 patients	Chronic refractory wounds (lower extremity)	2 mL allogeneic PRP was evenly injected into the wound surface	Allogeneic PRP is an effective and safe adjuvant treatment for chronic wounds, as demonstrated by the present study, which demonstrates that the combination of standard care and allogeneic PRP significantly reduces

						healing time for chronic wounds.
Monei b, 2018¹⁶	Egypt	Comparative study	40 patients	Chronic venous leg uclers (lower extremity)	Intradermal and subdermal injection of 2-4 mL PRP weekly, in all edges and in the granular floor of the ulcer for 6 sessions	The utilization of platelet-rich plasma represents a secure and noninvasive therapeutic approach in the management of chronic venous leg ulcers.

Lin, et al (2023)¹¹ showed that the combination of PRF and AgNP dressing demonstrates significant efficacy in the treatment of chronic refractory wounds. This treatment approach effectively alleviates patients' pain and local inflammation, enhances wound healing rates, shortens healing time, and reduces the risk of infection spread and complications.

Helmy, et al (2021)¹² enrolled study with eighty patients presenting with chronic venous leg ulcers. Forty patients were randomly assigned to receive autologous platelet-rich plasma (PRP) treatment. Inject intradermal and subdermal PRP with a 27-gauge syringe weekly for 4-6 sessions into the ulcer's margins and granular floor. This study demonstrates that PRP is an effective and significant wound repair agent for chronic leg venous ulcers. PRP is a straightforward, secure, and easy-to-learn technique.

Pires, et al (2021)¹³ At the conclusion of the 12-week treatment period, both the PRP (P = 0.0078) and control groups (P = 0.01) experienced a reduction in wound infections. The microorganisms were susceptible to the vast majority of antimicrobials tested. The PRP did not increase the amount of bacteria in the incisions. All identified S. aureus strains had biofilm-forming capabilities and were categorized as feeble biofilm producers. 17 P. aeruginosa strains were classified as weak biofilm producers, 14 as moderate, and 8 as robust biofilm producers.

Tsai, et al (2019)¹⁴ showed wound healing improved in two weeks in two group (p = 0.0083). Patients with diabetes who received platelet-derived patch treatment and PRP injection experienced wound size reduction to <25% of the original area by the fourth week of treatment, and >90% of the subjects had lesions of <10% their original size in the last three weeks of the trial. In contrast, the wound area of control subjects treated with conventional advanced wound dressings remained between 25 and 50 percent of its initial size from the fourth week of treatment until the conclusion of the study. Statistically, the experimental group with the PRP patch healed significantly faster than the control group (p <0.001).

Liao, et al (2019)¹⁵ showed allogeneic PRP-treated group exhibited bright red granulation that bled readily and reduced inflammatory exudation thirty days after treatment. There were no rejection reactions observed. The rate of chronic lesion healing was significantly faster in the group treated with allogeneic PRP than in the control group. Allogeneic PRP is an effective and safe adjuvant treatment for chronic wounds, as demonstrated by the present study, which demonstrates that the combination of standard care and allogeneic PRP significantly reduces healing time for chronic wounds.

Moneib, et al (2018)¹⁶ showed substantial reduction in ulcer size when compared to conventional treatment (p-value = 0.01) post-PRP therapy resulted. The mean area of the ulcer changed by 4.92 ± 11.94 cm following PRP therapy and 0.13 ± 0.27 cm following conventional therapy. Similarly, the mean percentage improvement in the area of the ulcer following PRP therapy was 13.67% ± 28.06% and 67.6% ± 36.6% for conventional therapy. The patients unanimously reported a subjective alleviation of discomfort related to the ulcer.

DISCUSSION

Platelet-rich plasma (PRP) is a serum derived from an individual's own blood by the process of centrifugation. It is characterized by elevated levels of platelets, growth factors, and cytokines, all of which have the potential to facilitate the regeneration of stem cells and the remodeling of tissues. The possible reduction in ulcer recovery time with the use of platelet-rich plasma (PRP) as an adjunctive treatment could enhance patients' quality of life and alleviate the healthcare burden associated with wound management.^{12,13,19}

Studies show that PRP might help surgery wounds heal faster and have fewer infections. We still need to figure out the best way to give PRP, including the best depth and route, timing, dose, vehicle, frequency, and interval of use for all types of wounds, both chronic and acute. Platelet-rich plasma might help with medical wound care, but a single dose given during surgery doesn't seem to have a long-lasting effect on how quickly the wound heals. Additionally, using PRP does not get rid of the need to carefully figure out and treat the root cause of a recurring wound.^{19,20}

Platelets include a number of secretory granules that are essential to the proper functioning of the platelets. Granules can be divided into three distinct categories: solid granules, o granules, and lysosomes. Granules are the most common of the three types of granules found in platelets, with each platelet containing between fifty and eighty of them. Platelets are the building

blocks that are used in the aggregation process. Platelets accomplish their primary role of maintaining homeostasis through the following three processes: adhesion, activation, and aggregation. Platelets become activated when vascular lesions occur, and as a result, the granules on platelets release substances that encourage coagulation.^{3,21}

In recent years, scientific and technical research has brought fresh insights on platelets and their functions. Prior to these years, it was believed that platelets solely had a role in maintaining the blood's hemostatic balance. Platelets have been shown to contain a significant amount of growth factors (GFs) and cytokines, both of which have the potential to affect inflammation, angiogenesis, stem cell migration, and cell proliferation. PRP is a natural source of signaling molecules, and upon platelet activation in PRP, P-granules are degranulated and release GFs and cytokines that will modify the pericellular microenvironment. Some of the most important GFs released by platelets in PRP include vascular endothelial GFs, fibroblast GFs (FGFs), platelet-derived GFs, epidermal GFs, hepatocyte GFs, insulin-like GFs 1, 2 (IGF-1, IGF-2), matrix metalloproteinase 2, 9, and IL-8.^{6,21}

Moreover, platelets also accommodate several secretory cytoplasmic and lysosomal granules, microparticles, and exosomes, which release various factors as platelets secretome (GFs, cytokines, adhesive molecules, chemokines, and other signalling molecules) that significantly participate in wound repair mechanism. These secretomes regulate diverse biochemical, molecular, and cellular aspects of wound niche, such as inflammation, recruitment of neutrophils and macrophages, promoting angiogenesis, ECM formation, and tissue remodelling.^{19,22}

The platelet secretome consists of three distinct types of granules: α -granules, dense granules, and lysosomal granules. It is estimated that each platelet contains roughly 50-80 granules. The qualities of this substance have made significant advancements in the field of regenerative medicine. The utilization of PRP in treatment of chronic wounds is a viable option due to its ability to create a structured network that concentrates platelets and leukocytes. This network facilitates the sustained release of numerous GFs that play a crucial role in promoting the healing process of wounds. The chronic wound or ulcer exhibits a diminished level of growth factor activity.¹⁹

One of the primary obstacles in the healing process of chronic wounds is the establishment of an effective wound matrix subsequent to debridement. The utilization of a platelet-derived patch is based on the principle of promoting the formation of a tissue network within the wound cavity through the interaction of platelet-rich plasma (PRP). This approach aims to enhance the development of the extracellular matrix, facilitate the process of granulation, and ultimately achieve epithelialization. While the utilization of platelet-derived patches for wound healing is not a new concept, the benefits associated with this therapy have only lately gained recognition.¹⁶

Clinical use of allogeneic PRP for chronic wounds should consider the following. Allogeneic PRP from donor blood must be tested beforehand to prevent blood-borne infections. Second, the PRP extraction procedure must follow operational guidelines, be sterile, and maintain platelet concentration. Chronic diseases must be managed to treat wounds. For big, resistant wounds with low blood supply, debridement, vacuum suction, and wound skin grafting may be best. After infection debridement, PRP should be administered to wounds with suppurative infections.

CONCLUSION

Platelet-rich plasma (PRP) is composed of several components obtained from platelets, including growth factors and cytokines. These bioactive substances have a significant role in modulating processes such as inflammation, angiogenesis, stem cell activity, and cellular proliferation. We still need to figure out the best way to give PRP, including the best depth and route, timing, dose, vehicle, frequency, and interval of use for all types of wounds, both chronic and acute.

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