



Platelet-rich plasma therapy for chronic cutaneous wounds stratified by etiology: a systematic review of randomized clinical trials

Verónica Salgado-Pacheco^{1,2,3} · Montserrat Serra-Mas^{1,4} · Marta Otero-Viñas^{1,2} 

Accepted: 26 December 2023 / Published online: 28 February 2024
© The Author(s) 2024

Abstract

Background Chronic wounds are a worldwide problem. One advanced biological therapy is platelet-rich plasma (PRP). Many studies have demonstrated the efficacy of PRP therapy in chronic wounds of different etiologies, but results are not conclusive.

Objective This systematic review intends to identify high-level clinical trials or randomized controlled trials (RCTs) that compare autologous platelet-rich plasma with alternative treatments for chronic cutaneous wounds in humans. Moreover, it investigates whether patients who have received autologous PRP therapy for chronic wound care for diverse etiologies have a better clinical outcome than patients treated with alternative treatments.

Methods PubMed, Scopus, Web of Science (WOS), The Cochrane Library, and Cumulative Index of Nursing and Allied Literature Complete (CINAHL) were searched in May 2021. The search was performed without any restriction. The studies were selected and reviewed by two authors on the basis of predefined inclusion criteria and following PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines, and a third author was consulted in the event of disagreement. All of the studies included were assessed using the Study Quality Assessment Tool for Controlled Intervention Studies published by the National Heart, Lung, and Blood Institute (NIH, USA).

Results Of the 2686 studies identified in the search, 16 RCTs met the inclusion criteria. Of the studies included, nine deal with diabetic wounds, five with venous wounds, one with arterial wounds, and one with pressure wounds. The studies included showed different PRP obtention and application methods due to a lack of standardized clinical guidelines. All studies dealing with venous ulcers showed an increase in wound healing among patients treated with PRP compared with the control group. Diabetic wound trials are non-conclusive due to the heterogeneity of the reported results. Only one study of arterial and one of pressure ulcers were identified, so no comparison can be made. Most of the articles included in the study had an unclear or low risk of bias, except in sample size power calculation.

Conclusions PRP may improve the healing of venous ulcers; however, there is no strong evidence regarding this positive effect in other wound etiologies. Although autologous PRP therapy is widely used, its effectiveness according to wound etiology is still not clear. The heterogeneity of the protocols to prepare and apply PRP therapy and the different methods for measuring chronic wound outcomes hinder the comparison of studies, thereby limiting the possibility of conducting a more robust analysis.

The systematic review was prospectively registered with PROSPERO under number CRD42021251501.

✉ Montserrat Serra-Mas
montserrat.serra@uvic.cat

✉ Marta Otero-Viñas
marta.otero@uvic.cat

¹ Tissue Repair and Regeneration Laboratory (TR2Lab), Institut de Recerca i Innovació en Ciències de la Vida i de la Salut a la Catalunya Central (IrisCC), Ctra. de Roda, 70 08500 Vic, Barcelona, Spain

² Department of Biosciences, Faculty of Science, Technology and Engineering, University of Vic - Central University

of Catalonia (UVic-UCC), C. de la Laura, 13, 08500 Vic, Barcelona, Spain

³ Medicine and Biomedical Sciences, Doctoral School, University of Vic - Central University of Catalonia (UVic-UCC), C. Dr. Junyent, 1 08500 Vic, Vic, Spain

⁴ Department of Experimental and Methodological Sciences, Faculty of Health Sciences and Welfare, University of Vic - Central University of Catalonia (UVic-UCC), C. Sagrada Família, 7, 08500 Vic, Spain

Key Points

Autologous PRP is widely used in chronic wounds treatment, but its effectiveness related to wound etiology is not clear.

There is not a standardized clinical protocol for preparation and application of PRP, which limits the comparison between studies.

Outcomes for measuring wound healing are not consistent across all articles; therefore, results comparison between them becomes challenging.

Introduction

Chronic wounds are cutaneous wounds that do not heal or require a long time to heal and often recur. These wounds are becoming more frequent due to population aging and increasing comorbidities [1, 2]. The management of chronic wounds poses an important and growing challenge to health systems worldwide, as they reduce patient quality of life and impose a significant economic burden [2].

The physiological process of wound healing includes a complex series of events starting after a skin breakage and ending with the successful closure of the wound, maintaining the integrity and the functionality of the skin. This process involves four sequential and overlapping phases: hemostasis/coagulation, inflammation, proliferation, and remodeling. However, several pathological conditions can alter this efficient and well-regulated process, leading to a delay in wound healing or even failure to heal; hence, wounds become chronic [3, 4]. Causes of chronic wounds include local wound factors (infection, persistent inflammation, and presence of necrotic tissue) and other clinical or social conditions of the patient (aging, frailty, hypoperfusion, presence of vascular diseases, diabetes, obesity, malnutrition, excessive pressure, immunosuppression, severe burns, or malignancy) [4, 5]. Although chronic wound causes are rather heterogeneous, an essential factor to select the appropriate wound treatment is the wound origin, known as etiology, including venous, diabetic, pressure, and arterial ulcers [4].

Venous ulcers affect 0.7–2.4% of the adult population, increase with aging, and are the most common chronic lower limb ulcers. About 70% of limb ulcers are caused by venous diseases. These ulcers are characterized by being superficial, tend to have irregular edges, and recur frequently. The main cause of venous ulcers is venous hypertension involving inadequate venous reflux or vein obstruction. The use of compression bandages is the most effective treatment to heal venous ulcers [6, 7].

Diabetic ulcers are the most deeply studied types of chronic wounds because they appear frequently in diabetic patients. These ulcers account for 1% of chronic wounds, and they are the most frequent cause of lower limb amputation [6]. The main causes of diabetic ulcers are neuropathy, hyperglycemia, mechanical pressure, and peripheral vascular disease [7]. Better control of diabetes contributes to the prevention of this kind of ulcer [8].

About 0.02% of the population is affected by pressure ulcers (PU). These ulcers are a common problem among patients with limited mobility and their prevalence ranges from 3% to 32% in patients with chronic wounds [9]. The main causes of PU are sustained pressure to an area of skin but also shear, friction, moisture, and poor nutrition [9]. The best treatment for PU is prevention, by continuously repositioning the patient. However, once the PU appears, the appropriate treatment depends on ulcer severity and the patient's clinical conditions. Some PU treatments are conventional dressing, growth factor-rich therapies, vacuum therapies, and surgical reconstruction [9].

Arterial wounds account for around 2.2% of leg ulcers, but this prevalence might increase considering that they are commonly mixed with other etiologies such as diabetic or venous ones [10]. These wounds are caused by peripheral arterial disease, usually resulting from atherosclerosis, diabetes, or other pathologies. This type of ulcer develops on the lateral side of the lower leg (dorsum of the foot or toes) in which blood supply to the affected areas is poor [4, 11]. Arterial wounds heal when leg revascularization is achieved through surgical procedures such as arterial bypass or angioplasty [10].

Chronic wound healing has been the focus of research over the years. However, even with the development of advanced therapies, a percentage of chronic wounds still do not heal [4].

Autologous platelet-rich plasma (PRP) therapy has been under investigation for the last 30 years and is being used clinically to manage chronic wounds [11]. This therapy is based on an enriched preparation of patients' growth factors and platelets to support the healing process. Although this technique has been widely used due to its simplicity, there is still no clear evidence of its effectiveness. Whereas activated PRP preparation is a relatively simple process, not all clinical settings use the same protocol to prepare and apply this therapy, which interferes in the comparison of clinical trials [12].

Autologous PRP therapy application is increasing in clinical wound units because of the healthcare and social impact of chronic cutaneous wounds and the limited outcomes of these wounds with current treatments. Recently, several systematic reviews have evaluated the published data on autologous PRP efficacy in chronic wound management [11]. However, most of them do not focus on clarifying the effect of autologous PRP therapy according to wound etiology. This systematic review aims to study the reported

evidence regarding the efficacy of autologous PRP application for chronic wounds according to their etiology.

Materials and methods

This systematic review was retrospectively registered with PROSPERO under number CRD42021251501.

Search strategy

PubMed, Scopus, Web of Science (WOS), The Cochrane Library, and Cumulative Index of Nursing and Allied Literature Complete (CINAHL) were searched in May 2021 to find reports of randomized controlled trials (RCTs) of relevance. No restrictions with respect to language or date of publication were imposed. Search strategy can be consulted in Fig. S1.

Inclusion and exclusion criteria

The studies included were clinical non-randomized studies and RCTs that compared autologous PRP with alternative treatments for chronic cutaneous wounds in humans. The studies excluded : (1) had no control group, (2) did not describe wound etiology, (3) had a sample size of fewer than 20 patients, (4) had a patient dropout rate higher than 15%, (5) dealt with non-human research, (6) included only traumatic or acute wounds, (7) applied non autologous PRP therapy, (8) were not published, (9) were conference abstracts or letters, and (10) consisted of reviews or systematic reviews.

Study selection

After the search, titles, abstracts, and full-text articles were screened independently by two reviewers (M.S-M and V.S-P) on the basis of predefined inclusion criteria and following Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [13]. In case of disagreement between the review authors, a third senior researcher (M.O-V) was consulted to obtain a consensus and solve the conflict. Only studies in English and whose full text was available were selected.

Data extraction

Both reviewers (M.S-M and V.S-P), independently, extracted from all selected studies, if present, the following data: (1) trial characteristics (design and sample size), (2) participants

by treatment group (number, age, sex, ethnicity, wound etiology, wound size, wound volume, and length of follow-up), (3) intervention (type of treatment and duration of therapy), (4) comparison condition (alternative treatment), and (5) outcome measures. The extracted details of the studies were recorded using a data extraction sheet.

Assessment of quality of evidence

The quality of the studies was assessed using the Study Quality Assessment Tool for Controlled Intervention Studies published on the National Heart, Lung, and Blood Institute (NIH, USA) website [14]. All studies included were independently assessed for the risk of bias by the two review authors (M.S-M and V.S-P). In the case of disagreement, a third reviewer (M.O-V) was involved in the decision.

Results

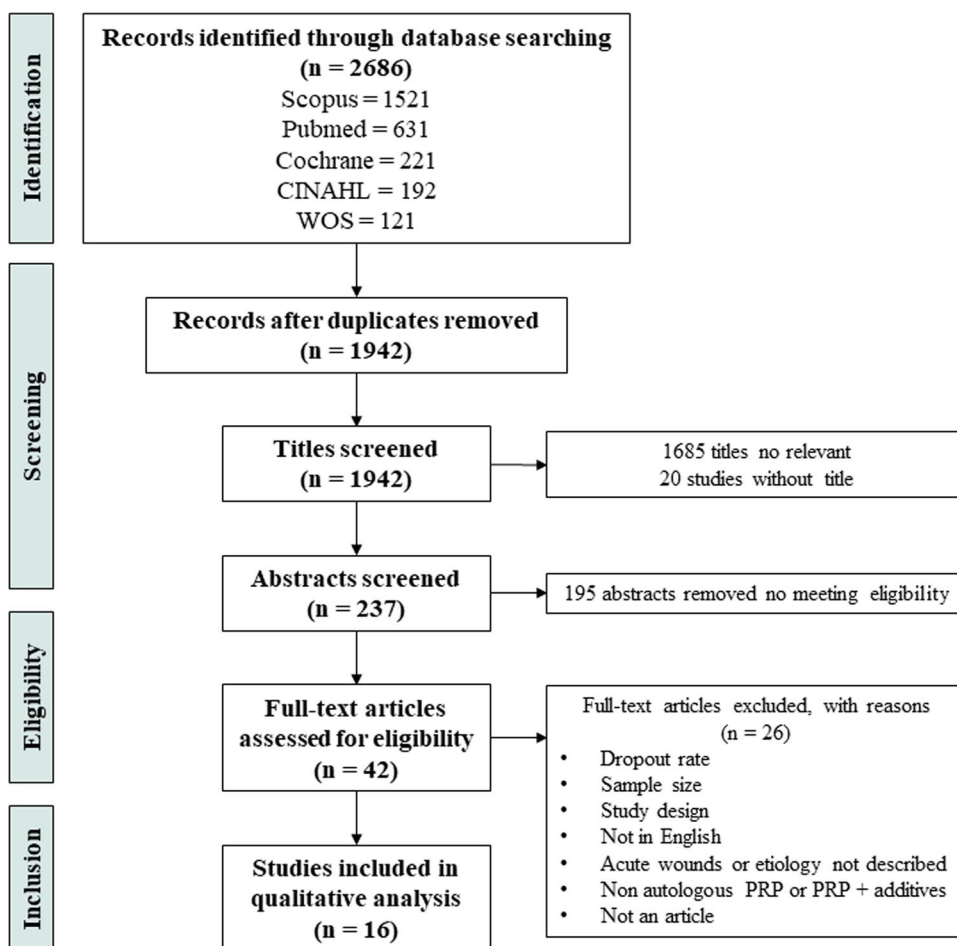
The primary search identified 2686 studies. After analyzing titles and abstracts, we ended up with 42 potentially relevant full-text articles. These articles were reviewed according to the inclusion and exclusion criteria and the final selection included 16 studies (Fig. 1), whereas 26 were excluded (Table S1).

Study characteristics

We extracted descriptive data from the 16 studies included (Table 1). In general, data from 1056 participants were included in this review, 488 participants received the control treatment, and 478 were treated with autologous PRP therapy. The missing 90 participants were treated with a different treatment; hence, they are not included in this review analysis [15–17].

The main goal of this review was to stratify the outcome of PRP treatment depending on wound etiology. Therefore, the studies were classified according to wound etiology: nine studies involved diabetic wounds [16–24], five venous ulcers [15, 25–28], one arterial wound [29], and one PU [30]. Selected clinical trials with diabetic foot ulcers included 560 participants, 264 participants receiving control treatment and 256 patients treated with autologous PRP [16–24]. Five studies analyzed the effect of autologous PRP in venous ulcers in 356 participants, 154 allocated to the control treatment group and 152 to the PRP treatment group [15, 25–28]. However, in one of the studies, PRP was applied topically in 30 patients and was injected in another 30 patients [15]. In this case, we excluded the data analysis from injected PRP therapy, and we only analyzed the results from the PRP topically administered so as to be consistent with all other studies included in this systematic review. The

Fig. 1 Study article selection flow diagram



clinical trial regarding the application of PRP therapy in arterial wounds included 80 patients; 40 patients were in the control treatment group, and 40 patients were infiltrated in the wound margins with autologous PRP [29]. The study on PRP treatment for PU included a total of 60 participants, divided equally between the control treatment group and the PRP treatment group [30].

Participants' description

In studies dealing with diabetic wounds, the mean age for the control group was 58 years, whereas, in the PRP group, the mean age was 56.2 years [16–23]. However, it should be noted that one of the studies dealing with diabetic wounds did not describe participants' age [24]. We identified two different groups of studies including venous etiology, four studies with participants younger than 50 years of age [15, 25–27], and another study where participants' mean age [28] was greater than 70 years. The study that analyzed PRP therapy in arterial wounds included participants with a mean age of 56 years [29], and in the study treating PU, the participants had a mean age of approximately 68 years [30].

Another important issue that caught our attention was participants' distribution by sex. In most of the papers included, the percentage of women was usually lower than that of men. The percentage of women in the studies concerning diabetic wounds ranged from 20% in the PRP group to 50% in the control group [21]. It is worth mentioning that, in Kakagia et al. [17], the percentage of women was higher than that of men (43.1% men versus 56.9% women), although it does not describe the distribution of participants between control and PRP groups. Observing the sex of the participants in the studies dealing with venous ulcers, women were clearly underrepresented in several studies [15, 25, 27], whereas in Stacey et al. [28], women were predominant in the control (52.3%) and PRP (64.3%) groups. The study by Helmy et al. [26] presented less women than men in both groups, but not with the high underrepresentation of the previously cited studies. Surprisingly, Moneib et al. [27] did not include a single woman in their control group. The study of PU has an equal distribution of women and men (52.4% women in the control group and 47.6% women in the PRP-treated group) [30], whereas the study of arterial ulcers had a significant deficiency of women among its participants (7.5% in the control group and 12.5% in the PRP group) [29].

Table 1 Included studies

| Study | Country | Etiology | Number of participants | | Age (years) | | Gender (%) | | | | Clinical outcomes | Follow-up period (months) |
|-----------------------------|-----------|----------|------------------------|-----|--------------|--------------|--------------------|------|------|------|---|---------------------------|
| | | | Control | PRP | Control | PRP | Control | | PRP | | | |
| | | | | | | | M | F | M | F | | |
| Ahmed et al., 2017 [18] | Egypt | Diabetic | 28 | 28 | 49.8 ± 15.4 | 43.2 ± 18.2 | 64.3 | 35.7 | 71.4 | 28.6 | Ulcer healed (%) Healing rate/week (cm ²) Infection (%) | 3 |
| Elsaid et al., 2019 [19] | Egypt | Diabetic | 12 | 12 | 55.6 ± 6.5 | 54.7 ± 6.6 | 50 | 50 | 66.7 | 33.3 | Reduction in ulcer size (%) Wound healing status | 5 |
| Gupta et al., 2021 [20] | India | Diabetic | 30 | 30 | 55.76 ± 10.2 | 56.03 ± 9.6 | 63.3 | 36.7 | 73.3 | 26.7 | Healed ulcer area (%) Healing rate (weekly) | 1.5 |
| He et al., 2020 [16] | China | Diabetic | 30 | 25 | 66.1 ± 12.1 | 64.6 ± 11.0 | 70 | 30 | 52 | 48 | Healing time Healing area/day Adverse reactions | * |
| Kakagia et al., 2007 [17] | Greece | Diabetic | 17 | 17 | 58 ± 10 | 57 ± 12 | 43.1 (M), 56.9 (F) | | | | Changes in wound dimensions (%) Complications Side effects | 2 |
| Karimi et al., 2016 [21] | Iran | Diabetic | 30 | 30 | ND | | 72 | 28 | 80 | 20 | Frequency of complete wound healing | 0.75 |
| Li et al., 2015 [22] | China | Diabetic | 58 | 59 | 64.1 ± 9.4 | 61.4 ± 13.1 | 65.5 | 34.5 | 62.7 | 37.3 | Wound healing grades Time to complete healing Wound healing rate Safety | 3 |
| Malekpour et al., 2021[23] | Iran | Diabetic | 47 | 43 | 56.7 ± 7.2 | 56.3 ± 7.1 | 63.8 | 36.2 | 60.5 | 39.5 | Healing time Need for amputation | 6 |
| Saad Setta et al., 2011[24] | Egypt | Diabetic | 12 | 12 | 40–60 | | ND | | | | Rate of healing Healing time | 3 |
| Elbarbary et al., 2020 [15] | Egypt | Venous | 30 | 30 | 41.80 ± 13.3 | 45.4 ± 9.35 | 80 | 20 | 86.7 | 13.3 | Rate of ulcer complete healing Percentage of ulcer area reduction Early treatment-related complications Ulcer recurrence Healing time | 12 |
| Elgarhy et al., 2020 [25] | Egypt | Venous | 20 | 20 | 43.5 ± 8.1 | 43.7 ± 13.12 | 90 | 10 | 80 | 20 | Rate of complete ulcer healing Percentage of ulcer area reduction Patient satisfaction | 1.5 |
| Helmy et al., 2021[26] | Egypt | Venous | 40 | 40 | 44 ± 11.4 | 48 ± 11 | 57.5 | 42.5 | 65 | 35 | Ulcer healed (%) Healing time | 12 |
| Moneib et al., 2018 [27] | Egypt | Venous | 20 | 20 | 32.5 ± 7.5 | 36.4 ± 10.2 | 100 | 0 | 95 | 5 | Improvement in ulcer area (%) | 1.5 |
| Stacey et al., 2000 [28] | Australia | Venous | 44 | 42 | 70 (26–92) | 72 (35–90) | 47.7 | 52.3 | 35.7 | 64.3 | Ulcers healed Adverse effects | 9 |

Table 1 (continued)

| Study | Country | Etiology | Number of participants | | Age (years) | | Gender (%) | | Clinical outcomes | Follow-up period (months) | |
|-------------------------------|---------|----------|------------------------|-----|---------------|-------------|------------|------|-------------------|---------------------------|---|
| | | | Control | PRP | Control | PRP | Control | PRP | | | |
| | | | | | | | | | | | M |
| Chandanwale et al., 2020 [29] | India | Arterial | 40 | 40 | 56.13 ± 11.38 | | 92.5 | 7.5 | 87.5 | 12.5 | 2 |
| Uçar et al., 2020 [30] | Turkey | Pressure | 30 | 30 | 67.8 ± 5.86 | 68.3 ± 6.37 | 48.7 | 52.4 | 51.3 | 47.6 | 2 |

F female, M male, PUSH Pressure Ulcer Scale for Healing, ND not described

*Until wound closure, surgical operation, or amputation

A surprising aspect observed in this systematic review is the geographic distribution of these clinical trials using autologous PRP therapy. Seven clinical trials were performed in Egypt [15, 18, 19, 24–27], two in China [16, 22], two in India [20, 29], and two in Iran [21, 23]. The remaining three trials were performed in other countries: Australia [28], Greece [17], and Turkey [30].

Preparation and application of PRP

PRP preparation includes several steps: blood extraction, PRP separation by centrifugation, and platelet activation. Significant differences in autologous PRP therapy preparation were observed in the analysis of the articles included (Table 2) [18]. Although most of the studies used citrate as an anticoagulant for blood collection, in Stacey et al. [28] ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant, and the other three studies do not specify which type was used [18, 22, 29]. For PRP fraction isolation, there is also great variability between the studies on spin cycles (either centrifugation time or speed) used to separate platelets from the rest of the blood (Table 2). In terms of PRP activation and application, relevant differences were also identified. Some authors describe a platelet activation step using thrombin and/or calcium before applying PRP therapy, whereas others do not mention any procedure for PRP activation [20, 21, 29, 30]. As described in Table 2, PRP formulation was activated with calcium ions in eight trials [15, 16, 19, 22–25, 27], and thrombin was used in combination with calcium in four of the studies [16, 22–24]. In Stacey et al. [28] PRP preparation is quite different from other studies because they do not use the patient's plasma for resuspension but use PBS buffer, also aliquoting the preparation. These aliquots were stored at -20°C prior to use. Conversely, the remaining authors prepare PRP immediately before being applied to the wound bed. It should be noted that Kakagia et al. [17] do not include any information about PRP preparation, activation, and application.

Additionally, the studies included show differences in the PRP application protocol, including topical PRP gel application, PRP injection, or both procedures together (Table S2).

Healing outcomes according to wound etiology

The main aim of this work is to analyze the efficacy of PRP treatment for complex wounds according to their etiology. For this reason, we classified the clinical trials included on the basis the etiology of the treated wounds.

Diabetic ulcers

The results of the study by Saad Setta et al. [24] show 75% of healed wounds in the control group and 100% healed

Table 2 PRP preparation

| Study | Etiology | Anticoagulant | Anticoagulant volume | Blood volume (ml) | First spin | | Second spin | | Resuspension volume | Activation PRP |
|-------------------------------|----------|---|-------------------------------------|-------------------|------------|------------|-------------|------------|---------------------|---|
| | | | | | Speed | Time (min) | Speed | Time (min) | | |
| Ahmed et al., 2017 [18] | Diabetic | ND | ND | 20 | 1500 rpm | 5 | 3500 rpm | 5 | 3 ml plasma | ND |
| Elsaid et al., 2019 [19] | Diabetic | ND | ND | 20 | 3600 rpm | ND | 2400 rpm | ND | ND | 20% CaCl ₂ |
| Gupta et al., 2021 [20] | Diabetic | Sodium citrate tube | ND | 20 | 2500 rpm | 5 | ND | ND | ND | ND |
| He et al., 2020 [16] | Diabetic | Acid citrate dextrose solution B anticoagulants | ND | 50–100 | 600 rpm | 15 | 1135 g | 7 min | ND | 1000 IU thrombin + 1 ml 10% Ca-gluconate in proportion 10:1 (v/v) with PRP |
| Kakagia et al., 2007 [17] | Diabetic | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Karimi et al., 2016 [21] | Diabetic | Sodium citrate | 3 ml | 30 | 200 rpm | 10 | ND | ND | 5 ml | ND |
| Li et al., 2015 [22] | Diabetic | Anticoagulant pH 8 | 2–10 ml | 20–100 | 313 g | 4 | 1252 g | 6 | ND | Thrombin + calcium + gluconate (10:1) (v/v) |
| Malekpour et al., 2021 [23] | Diabetic | Citrate dextrose | ND | 20 | 1500 rpm | 5 | 3500 rpm | 5 | 3 ml plasma | 0.2 ml thrombin/1 ml PRP + CaCl ₂ |
| Saad Setta et al., 2011 [24] | Diabetic | Citrate dextrose | ND | 10 | 1007 g | ND | 447.5 g | ND | 20% bottom | 0.2 ml thrombin/1 ml PRP + 0.1 ml CaCl ₂ 10% CaCl ₂ 10% 1:4 ratio |
| Elbarbary et al., 2020 [15] | Venous | Sodium citrate 3.8% | 5 ml | 20–45 | 2500 rpm | 10 | 3500 rpm | 5 | ND | CaCl ₂ 10% 1:4 ratio |
| Elgarhy et al., 2020 [25] | Venous | Sodium citrate | 10:01 | 20 | 1372 g/min | 15 min | ND | ND | ND | 0.1 ml CaCl ₂ /ml PRP |
| Helmy et al., 2021 [26] | Venous | Citrate tubes | 9 parts of blood:1 of anticoagulant | ND | Soft spin | ND | Hard spin | ND | 2–4 ml plasma | Plastic tube |
| Moneib et al., 2018 [27] | Venous | Acid citrate dextrose | ND | 10 | 277 g | 10 | 277 | 5 | ND | 0.1 ml Ca-gluconate to 1 ml PRP |
| Stacey et al., 2000 [28] | Venous | EDTA | ND | 70 | 500 rpm | 70 | 3000 | 10 | 4 ml PBS | ND |
| Chandanwale et al., 2020 [29] | Arterial | ND | ND | ND | 1200 rpm | 10 | 2000 | 10 | 2–4 ml plasma | ND |
| Uçar et al., 2020 [30] | Pressure | Sodium citrate | 3 ml | 10 | 2000 rpm | 5 | ND | ND | ND | ND |

ND not described, CaCl₂ calcium chloride, PRP platelet-rich plasma, EDTA ethylenediaminetetraacetic acid

Table 3 Wound healing percentage at the end of the study

| Study | Etiology | Control group | PRP group |
|-------------------------------|----------|---------------|-----------|
| Ahmed et al., 2017 [18] | Diabetic | 68 | 86 |
| Elsaid et al., 2019 [19] | Diabetic | 0 | 25 |
| Gupta et al., 2021 [20] | Diabetic | 16.6 | 20 |
| He et al., 2020 [16] | Diabetic | ND | |
| Kakagia et al., 2007 [17] | Diabetic | 11.8 | 11.8 |
| Karimi et al., 2016 [21] | Diabetic | 40 | 36 |
| Li et al., 2015 [22] | Diabetic | 69 | 84.8 |
| Malekpour et al., 2021 [23] | Diabetic | ND | |
| Saad Setta et al., 2011 [24] | Diabetic | 75 | 100 |
| Elbarbary et al., 2020 [15] | Venous | 46.7 | 66.7 |
| Elgarhy et al., 2020 [25] | Venous | 0 | 80 |
| Helmy et al., 2021 [26] | Venous | 47.5 | 85 |
| Moneib et al., 2018 [27] | Venous | 0 | 35 |
| Stacey et al., 2000 [28] | Venous | 77.3 | 78.6 |
| Chandanwale et al., 2020 [29] | Arterial | ND | |
| Uçar et al., 2020 [30] | PU | ND | |

ND not described, PU pressure ulcer

wounds in the PRP treatment group. Two studies [18, 22] show similar behavior in wound healing percentage even though the included patients did not belong to the same age group (control: 68–69% healing, PRP treatment: 84.8–86% healing, respectively). In Elsaid et al. [19] there are no healed wounds in the control group versus 25% in the PRP treatment group. The other diabetic wounds trials [17, 20, 21] showed non-conclusive results (Table 3). Furthermore, data concerning neuropathy, glycemic control, diabetes duration, and osteomyelitis, which are essential factors in the management of diabetic foot ulcers, are displayed in Table S3. However, these diabetic conditions show no clear association with the wound healing percentage in the reviewed trials. Additionally, the diabetic studies [17, 19, 21] with the lowest percentage of wound healing are those with the largest wound initial area. This trend is also evident in the study by Elgarhy et al. [25], suggesting that the wound area at the beginning of the treatment could influence the therapy result (Table S4).

Venous ulcers

All the studies concerning venous ulcers show an increase in wound healing percentage using PRP treatment compared with the control group (Table 3). Two of studies included in the analysis present a greater increase in wound healing percentage when using PRP therapy [26, 27] in comparison with other studies. A further two studies [16, 28] also show a moderate increase in wound healing percentage using PRP

treatment versus control. The study by Stacey et al. [29] shows the smallest increase in wound healing compared with the control group. It is interesting to note that in Elgarhy et al. [26] not a single wound healed in the control group after 3 months of follow-up.

Other etiologies

In the studies included in this work, there was only one trial dealing with arterial ulcers and another concerning PU. We cannot identify a trend in the use of PRP therapy for these types of chronic wounds, as there is not enough basis for comparison.

The arterial wound study [29] does not describe the percentage of healed wounds. Instead, they show a decrease in wound area to a higher rate in patients treated with PRP than in the control group. The study describes that the mean reduction of the surface area of the wounds after 60 days was 66.22% in the treatment group, while in the control group the mean reduction was 29.89% (Table 3).

PU are a very different type of wound, and in the study by Uçar et al. [30], they use the PUSH score to validate the improvement of ulcers with PRP application. In this study, they describe a statistically significant improvement in wounds treated with PRP compared with control after 2 months.

Quality assessment

The risk of bias in autologous PRP therapy studies can be seen in Figs. 2 and 3. An unclear risk of bias was marked in this instance where the article lacked specific parameters, which rendered it impossible to ascertain whether the risk of bias is high or low magnitude. The risk of selection bias, which includes adequate sequence generation and allocation concealment, was considered low in 12 trials [15, 17, 19–22, 24–26, 28–30] and unclear in the other four studies [16, 18, 23, 27]. In reference to performance and detection bias, most studies did not specify whether the participants, personnel, and assessor were blinded. In only 2 of the 16 studies [21, 28] were participants and personnel blinded, and in 5 trials out of 16 [15, 18, 22, 25, 28], the assessors were blinded. Three studies [15, 19, 25] have a high risk of bias due to participants and personnel not being blinded. In addition, another study [19] specified that the assessors were not blinded.

Of 16 trials, 15 [15–23, 25–30] were rated as having a low risk of bias because the groups of patients were reported to be similar at baseline, the overall dropout rate was less than 20%, and there was high treatment adherence. Two trials [18, 24] did not reveal whether the differential dropout rate was 15% or less between groups.

Fig. 2 Overall quality assessment

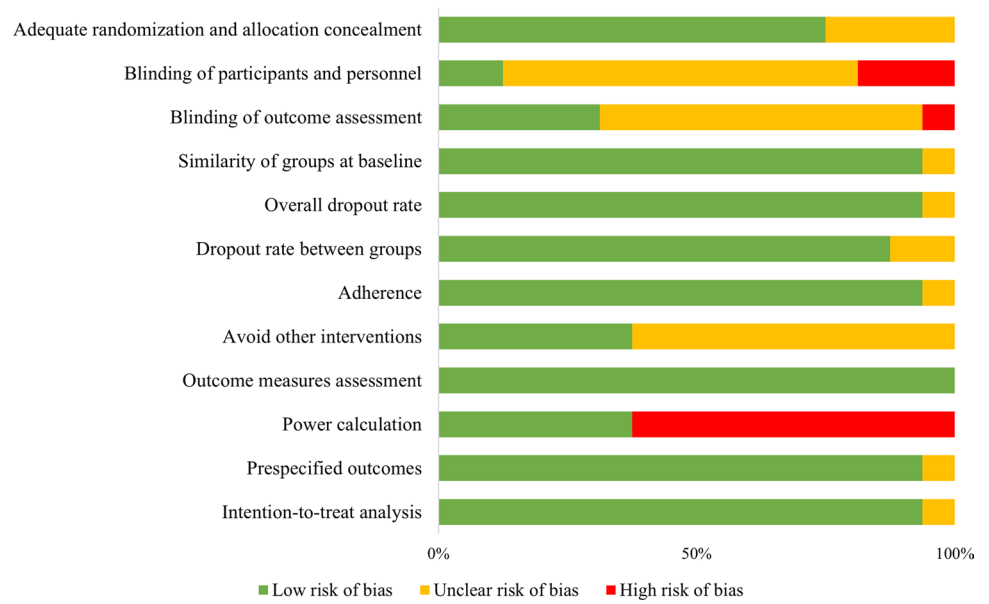


Fig. 3 Studies' quality assessment

Moreover, only eight studies [15, 16, 18, 21–23, 26, 28] guaranteed that other clinical interventions were avoided. All trials used consistent, valid, and reliable measures across all study participants to assess the outcomes, hence they have a low risk of bias in this aspect. Most of the studies, 10 of 16 [16–18, 20, 23–27, 30], have a high risk of bias concerning reporting that sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power. The risk of bias of prespecified outcomes and intention-to-treat analysis were rated as low in 15 trials [15, 17–30], and one was unclear [16]. In general, all articles, except the one by Saad Setta et al. [24], are of good quality and present a low risk of bias.

Discussion

In this work we have collected 16 randomized clinical trials concerning the use of autologous PRP therapy for chronic wound treatment. The purpose of this systematic review was to evaluate the efficacy of autologous PRP therapy in chronic wound healing considering wound etiology. Even though some of the results are significantly positive, the substantial diversity of studies included within trials regarding wound etiologies, age of participants, and other features of PRP therapy does not allow us to provide a decisive conclusion.

Chronic wounds are an increasing problem worldwide due to the aging of the population, but in the studies included, the patients were especially young in all of them in comparison with other studies published [4]. In fact, it has been described that younger patients have a better general health status than older, fragile patients and thus may experience a better wound healing outcome [5]. Additionally, the study by Stacey et al. [28] that included older patients than the other studies showed the smallest increase in wound healing compared with the control group. This data suggests that patients' aging might impact the likelihood of wound healing [31]. The healing outcomes described in the studies included in this systematic review exhibit heterogeneity. Therefore, it is difficult to compare the percentage of healed wounds with ulcer size reduction or healing time. Forthcoming clinical trials may do well to consider reporting all these outcomes. Furthermore, the varying proportion of men and women included in the reviewed trials presents challenges in comparing studies and analyzing the potential relationship between gender and the percentage of healing [32].

There are no established clinical guidelines for PRP preparation and application in chronic wounds, and this was confirmed by analyzing the PRP protocols in all the included studies. Some of the studies apply the activated PRP topically as a platelet gel, while others do so as PRP dressing

[15, 16, 18, 21–23, 30] and whereas, in others, activated PRP was injected [26, 29] or both management strategies were implemented [15, 26]. This lack of a specific clinical procedure makes it difficult to compare the results of the therapy between studies. Altogether, this data suggests that the efficacy of the PRP therapy might depend on both the procedure of PRP preparation and application (topical or injected) [33]. Confirming the results of other systematic reviews [11, 12, 34], none of the studies in this review report any adverse effects due to PRP topical application or injection. This also assures the safety of this therapy on the health status of the patients where this therapy is going to be used.

Due to inclusion and exclusion criteria, we ended up with only one study about PU [30] and one clinical trial on arterial ulcers [29]. Therefore, their results could not be compared with any other studies, and no conclusions about the efficacy of PRP therapy could be provided due to a lack of evidence in these etiologies. On the other hand, we found five trials on venous ulcers [15, 25–28] and nine on diabetic ulcers [16–24], permitting their comparison. According to etiology, our results looking at PRP application in cases of diabetic ulcers do not show the clear positive effect on ulcer healing described in a previous systematic review [34] because the results are not consistent within all the studies analyzed [17, 21]. This observation might be attributable to the inherent variability of clinical conditions of diabetic patients, such as arteries affection, glycemic control, diabetes mellitus duration, or presence of osteomyelitis. In patients with venous ulcers, treatment with PRP increased the percentage of healed wounds in all studies analyzed in this review. However, the earliest published study concerning venous ulcers showed the lowest wound healing percentage and used a substantially different PRP preparation protocol compared with the others [28].

For our review to gain rigor and robustness, our exclusion criteria had considered the dropout rate and discarded studies with fewer than 20 participants. Even though we took technical aspects into consideration in the design and performance of the clinical trials included, the results are not sufficiently conclusive.

The analysis of the overall quality of the clinical trials included showed a low risk of bias in most of the parameters analyzed: randomization and allocation concealment, similarity of groups at baseline, adherence to treatment, dropout rate (overall and between groups), intention-to-treat analysis, and assessment of the outcomes. However, power calculation of the studies included showed a high risk of bias due to poor reporting data and lack of clinical trial design details. Moreover, the samples were of inadequate size in most of the studies indicating that better-designed trials should be conducted to extrapolate the results to the general population.

According to the currently available literature [11, 12, 34], it is unclear whether PRP therapy is efficient for the treatment of chronic wounds according to their etiology. For arterial and PU, we could not find sufficient evidence concerning the efficacy of PRP treatment. As described before, for diabetic ulcers, it is unclear whether PRP therapy is effective, and our results indicate that this therapy would be effective in the treatment of venous ulcers. However, more clinical trials should be performed considering wound etiology heterogeneity, including more patients to achieve better statistical power. In addition, a standardized PRP preparation and application protocol should be considered so as to generate more reliable results and provide stronger conclusions about the effectiveness of this therapy in chronic wound healing. Also, the healing outcomes of the therapy should be recorded in a way that could be useful for comparing clinical trials.

According to the results observed in these reviewed studies, we would like to suggest the following essential points: (1) further research studies are needed to ascertain the standardized methodology for preparing and administering PRP therapy in chronic wounds, aimed at mitigating variability and increasing the reproducibility among studies; (2) larger clinical trials are required to elucidate the potential influence of factors such as age and gender on the efficacy of PRP therapy for treating chronic wounds; and (3) more systematic conducted RCTs with appropriately sized sample population are necessary to reliably generalize the results to the broader population.

Conclusions

The data from this systematic review indicate that autologous PRP therapy is both effective and safe in treating chronic wounds. PRP may improve the healing of venous ulcers. However, there is no strong evidence of this positive effect in other wound etiologies. Moreover, there is currently no standardized protocol for PRP therapy preparation, application, or even for evaluating its efficacy. In addition, the different methods of measuring chronic wound outcomes make it difficult to compare studies with one another, thereby limiting the possibility of conducting a more robust analysis. These heterogeneous results demonstrate the need for standardizing the aforementioned steps to obtain consistent conclusions about autologous PRP efficacy according to wound etiology.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40267-023-01044-7>.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature.

Declarations

Funding This work was supported by the PO FEDER of Catalonia 2014–2020 (project PECT Osona Transformació Social, Ref. 001-P-000382); the Instituto de Salud Carlos III through the project PI19/01379, co-funded by European Union (ERD/ESF, “A way to make Europe”/“Investing in your future”); and the predoctoral fellowship of University of Vic – Central University of Catalonia (2020-21).

Conflicts of Interest The authors declare no conflict of interest.

Availability of Data and Material The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Ethics Approval Not applicable

Consent to Participate Not applicable

Consent for Publication Not applicable

Code Availability Not applicable

Author Contributions Conception and design: M.S-M, V.S-P, and M.O-V. Data acquisition: M.S-M and V.S-P. Data analyses and interpretation: M.S-M, V.S-P, and M.O-V. Drafting main manuscript: V.S-P. Revision: M.S-M and M.O-V. Funding support: M.O-V. All authors read and approved the final manuscript.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. Goswami AG, Basu S, Shukla VK. Wound healing in the golden agers: what we know and the possible way ahead. *Int J Low Extrem Wounds*. 2022;21:264–71.
2. Olsson M, Järbrink K, Divakar U, et al. The humanistic and economic burden of chronic wounds: a systematic review. *Wound Repair Regen*. 2019;27:114–25.
3. Wang PH, Huang BS, Horng HC, et al. Wound healing. *J Chin Med Assoc*. 2018;81:94–101.
4. Falanga V, Isseroff RR, Soulika AM, et al. Chronic wounds. *Nat Rev Dis Primers*. 2022;8:50.
5. Espauella-Ferrer M, Espauella-Panicot J, Noell-Boix R, et al. Assessment of frailty in elderly patients attending a multidisciplinary wound care center: a cohort study. *BMC Geriatr*. 2021. <https://doi.org/10.1186/s12877-021-02676-y>.
6. Bowers S, Franco E. Chronic wounds: evaluation and management. *Am Fam Physician*. 2020;101:159–66.

7. Dixon D, Edmonds M. Managing diabetic foot ulcers: pharmacotherapy for wound healing. *Drugs*. 2021;81:29–56.
8. Lim JZM, Ng NSL, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med*. 2017;110:104–9.
9. Boyko TV, Longaker MT, Yang GP. Review of the current management of pressure ulcers. *Adv Wound Care (New Rochelle)*. 2018;7:57–67.
10. Khanna AK, Tiwary SK. Ulcers of the lower extremity. *Ulcers of the lower extremity*. 2016;1–479.
11. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. *Cochrane Database Syst Rev*. 2016. <https://doi.org/10.1002/14651858.CD006899.pub3>.
12. Burgos-Alonso N, Lobato I, Hernández I, et al. Adjuvant biological therapies in chronic leg ulcers. *Int J Mol Sci*. 2017;18(12):2561.
13. Asar Sh, Jalalpour Sh, Ayoubi F, et al. PRISMA; preferred reporting items for systematic reviews and meta-analyses. *J Raf Univ Med Sci*. 2016;15:68–80.
14. Study quality assessment tools | NHLBI, NIH. [cited 2022 Nov 28]. Available from: <https://www.nlm.nih.gov/health-topics/study-quality-assessment-tools>
15. Elbarbary AH, Hassan HA, Elbendak EA. Autologous platelet-rich plasma injection enhances healing of chronic venous leg ulcer: a prospective randomised study. *Int Wound J*. 2020;17:992–1001.
16. He M, Guo X, Li T, et al. Comparison of allogeneic platelet-rich plasma with autologous platelet-rich plasma for the treatment of diabetic lower extremity ulcers. *Cell Transplant*. 2020;29:096368972093142.
17. Kakagia DD, Kazakos KJ, Xarchas KC, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. *J Diabetes Complicat*. 2007;21:387–91.
18. Ahmed M, Reffat SA, Hassan A, et al. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017;38:206–11.
19. Elsaid A, El-Said M, Emile S, et al. Randomized controlled trial on autologous platelet-rich plasma versus saline dressing in treatment of non-healing diabetic foot ulcers. *World J Surg*. 2020;44:1294–301.
20. Gupta A, Channaveera C, Satyaranjan S, et al. Efficacy of intralesional platelet rich plasma in diabetic foot ulcer. *J Am Podiatr Med Assoc*. 2021. <https://doi.org/10.7547/19-149>.
21. Karimi R, Afshar M, Salimian M, et al. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. *Nurs Midwifery Stud*. 2016. <https://doi.org/10.17795/nmsjournal30314>.
22. Li L, Chen D, Wang C, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: a prospective, randomized clinical trial. *Wound Repair Regen*. 2015;23:495–505.
23. Malekpour Alamdari N, Shafiee A, Mirmohseni A, et al. Evaluation of the efficacy of platelet-rich plasma on healing of clean diabetic foot ulcers: a randomized clinical trial in Tehran, Iran. *Diabetes Metab Syndr*. 2021;15:621–6.
24. Saad Setta H, Elshahat A, Elsherbiny K, et al. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. *Int Wound J*. 2011;8:307–12.
25. Elgarhy LH, El-Ashmawy AA, Bedeer AE, et al. Evaluation of safety and efficacy of autologous topical platelet gel vs platelet rich plasma injection in the treatment of venous leg ulcers: a randomized case control study. *Dermatol Ther*. 2020;33: e13897.
26. Helmy Y, Farouk N, Ali Dahy A, et al. Objective assessment of platelet-rich plasma (PRP) potentiality in the treatment of chronic leg ulcer: RCT on 80 patients with venous ulcer. *J Cosmet Dermatol*. 2021;20(10):3257–63.
27. Moneib HA, Youssef SS, Aly DG, et al. Autologous platelet-rich plasma versus conventional therapy for the treatment of chronic venous leg ulcers: a comparative study. *J Cosmet Dermatol*. 2018;17:495–501.
28. Stacey MC, Mata SD, Trengove NJ, et al. Randomised double-blind placebo controlled trial of tropical autologous platelet lysate in venous ulcer healing. *Eur J Vas Endovasc Surg*. 2000;20:296–301.
29. Chandanwale KA, Mahakalkar CC, Kothule AK, et al. Management of wounds of peripheral arterial disease using platelet rich plasma. *J Evol Med Dent Sci*. 2020;9:2239–45.
30. Uçar Ö, Çelik S. Comparison of platelet-rich plasma gel in the care of the pressure ulcers with the dressing with serum physiology in terms of healing process and dressing costs. *Int Wound J*. 2020;17:831–41.
31. Sen CK. Human wound and its burden: updated 2022 compendium of estimates. *Adv Wound Care*. 2023;12:657–70.
32. Wilkinson HN, Hardman MJ. The role of estrogen in cutaneous ageing and repair. *Maturitas*. 2017;103:60–4.
33. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review. *EFORT Open Rev*. 2021;6:225–35.
34. Hu Z, Qu S, Zhang J, et al. Efficacy and safety of platelet-rich plasma for patients with diabetic ulcers: a systematic review and meta-analysis. *Adv Wound Care*. 2019;8:298–308.