

Technology Assessment Program

Platelet-Rich Plasma for Wound Care in the Medicare Population

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Platelet-Rich Plasma for Wound Care in the Medicare Population

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Key Messages

Purpose of review

To evaluate the effectiveness of autologous platelet-rich plasma (PRP) in individuals with lower extremity diabetic ulcers, lower extremity venous ulcers and pressure ulcers.

Key messages

- We are moderately confident that autologous platelet-rich plasma increases complete wound closure or healing (moderate strength of evidence [SOE]) in individuals with lower extremity diabetic ulcers. We have low confidence that autologous platelet-rich plasma may shorten time to wound closure (low SOE), and reduce wound size (low SOE). Evidence is insufficient to make conclusions about other important outcomes such as hospitalization, amputations and wound recurrence.
- Evidence is insufficient to make conclusions about the effect of autologous platelet-rich plasma on wound healing in individuals with lower extremity venous ulcers.
- Evidence is insufficient to make conclusions about the effect of autologous platelet-rich plasma on wound healing in individuals with pressure ulcers.
- There is no statistically significant difference in adverse events and serious adverse events between autologous platelet-rich plasma and management without autologous platelet-rich plasma, though the available literature does not evaluate and report adverse events consistently.
- The available literature suffers from important limitations, such as inadequate description of offloading and wound care procedures, wound characteristics, platelet-rich plasma formulation techniques, concentration and volume; inadequate length of followup and lack of stratification by comorbidities and other patient characteristics such as diabetes control, vascular perfusion and under representation of older adults.

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Food and Drug Administration (FDA) has not licensed any PRP products for any specific indications. If a medical device is labeled or promoted for manufacturing PRP for the purpose of administering the device output to a patient, then the device would require FDA approval or clearance for that use prior to marketing in the United States. A physician may use a cleared or approved medical device for the treatment of a particular patient in a manner that differs from the cleared or approved indication (known as off-label use).

This report is based on research conducted by the Mayo Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHS290201500013I). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Medicare & Medicaid Services requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: Mayo Clinic Evidence-based Practice Center (Contract Number: HHS290201500013I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Platelet-Rich Plasma for Wound Care in the Medicare Population

Structured Abstract

Objectives. To evaluate the effectiveness of autologous platelet-rich plasma (PRP) in individuals with lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers.

Data sources. MEDLINE, Embase, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, Scopus and various grey literature sources from database inception to June 11, 2020.

Review methods. We included randomized controlled trials (RCTs) and comparative observational studies that compared PRP to any other wound care without PRP in adult patients. Pairs of independent reviewers selected and appraised studies. Meta-analysis was conducted when appropriate and the strength of evidence (SOE) was determined based on a priori plan.

Results. We included 27 studies (22 randomized, 5 comparative observational studies, total of 1,796 patients). 15 studies enrolled patients with lower extremity diabetic ulcers, 11 enrolled patients with lower extremity venous ulcers, and 2 enrolled patients with pressure ulcers in any location. Followup after intervention ranged from no followup to 11 months. The available studies suffered from important limitations, such as inadequate description of offloading and wound care procedures, wound characteristics, platelet-rich plasma formulation techniques, concentration and volume; inadequate length of followup; and lack of stratification by comorbidities and other patient characteristics including older adults. Compared with management without PRP, PRP therapy increased complete wound closure or healing in lower extremity diabetic ulcers (RR: 1.20; 95% CI: 1.09 to 1.32, moderate SOE), shortened the time to complete wound closure, and reduced wound area and depth (low SOE), although Medicare-eligible older adults were underrepresented in the included studies. No significant changes were found in terms of wound infection, amputation, wound recurrence, or hospitalization. In patients with lower extremity venous ulcers, the SOE was insufficient to estimate an effect on critical outcomes, such as complete wound closure or time to complete wound closure. Similarly, evidence was insufficient to estimate an effect on any outcome in pressure ulcers. There was no statistically significant difference in death, total adverse events or serious adverse events between PRP and management without PRP.

Conclusions. Autologous platelet-rich plasma based on moderate SOE increases complete wound closure or healing, and low SOE shortens healing time and reduces wound size in individuals with lower extremity diabetic ulcers. The evidence is insufficient to estimate an effect of autologous platelet-rich plasma on wound healing in individuals with lower extremity venous ulcers or pressure ulcers.

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Evidence Summary

Main Points

- We are moderately confident that autologous platelet-rich plasma (PRP) increases complete wound closure or healing (moderate strength of evidence [SOE]) in individuals with lower extremity diabetic ulcers. We have low confidence that autologous platelet-rich plasma may shorten healing time (low SOE), and reduce wound size (low SOE). Evidence is insufficient to make conclusions about other important outcomes such as hospitalization, amputations and wound recurrence.
- Evidence is insufficient to make conclusions about the effect of autologous platelet-rich plasma on wound healing in individuals with lower extremity venous ulcers.
- Evidence is insufficient to make conclusions about the effect of autologous platelet-rich plasma on wound healing in individuals with pressure ulcers.
- There is no statistically significant difference in adverse events and serious adverse events between autologous platelet-rich plasma and management without autologous platelet-rich plasma, though the available literature does not evaluate and report adverse events consistently.
- The available literature suffers from important limitations, such as inadequate description of offloading and wound care procedures, wound characteristics, platelet-rich plasma formulation techniques, concentration and volume; inadequate length of followup, and lack of stratification by comorbidities and other patient characteristics, such as diabetes control, vascular perfusion and under representation of older adults.

Background and Objectives

Chronic wounds are a common chronic medical condition with a high impact on the aging population, with chronic wounds or infections affecting nearly 15 percent of Medicare beneficiaries with a healthcare burden of \$28 to \$96 billion United States dollars per year.¹ Conditions that are most commonly associated with wound formation include diabetes, pressure injuries, and venous or arterial diseases.

Autologous platelet-rich plasma is the fraction of blood plasma from a patient's peripheral blood that contains higher than baseline concentrations of platelets including concentrated growth factors and cytokines. PRP contains Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), Insulin Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor- β , and Hepatocyte Growth Factor (HGF), all of which have been shown to stimulate healing.² The contents of the platelet in PRP are either released through spontaneous activation upon exposure to collagen in the wounds,³ pre-released as PRP lysate by freeze-thawing disruption of platelet membrane,⁴ or pre-released by activation with degranulation triggered by thrombin and/or calcium chloride.⁵ PRP has attracted significant interest because platelets possess various growth factors that are critical for tissue repair and regeneration, and they have antibacterial properties in traumatic injuries.^{6,7}

PRP preparations are being offered typically in a point-of-care setting, delivered as a preparation of aqueous suspension obtained by centrifugation of whole blood or as a gel. PRP is most commonly applied to the wound bed with dressing, but can be injected in the wound bed.

This systematic review evaluates the overall effectiveness of treatment of lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers with PRP, as well as the impact of PRP content, carriers, dosage, frequency and duration of application.

Key Questions

Comparative Effectiveness Questions:

KQ 1. What are the benefits and harms of treatment strategies including PRP alone with or without other wound care treatments compared with other wound care treatments in patients with diabetic, venous and pressure chronic wounds, for patient oriented outcomes?

Contextual Questions:

KQ 2. What types of PRP preparations are currently being marketed in U.S. medical practices (gel, liquid, etc.)?

KQ 3. What PRP preparations are currently being investigated in ongoing trials?

Future Research Questions:

KQ 4. What best practices in study design could be used to produce high quality evidence on PRP?

KQ 5. What are the evidence gaps found in this body of research?

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews.⁸ The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.⁹ The study protocol is published on AHRQ website. (<https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/platelet-rich-plasma-protocol-amendment.pdf>) and registered in the international prospective register of systematic reviews (PROSPERO #: CRD42020172817).

Results

Literature Searches and Evidence Base

The literature search identified 4,147 citations. An additional 172 references were identified through reference mining, grey literature search; and from Technical Experts. There were 27 studies and 1,796 patients included in the systematic review. Of the 27 studies, 22 were randomized controlled trials (RCTs)¹⁰⁻³⁰ and 5 were comparative observational studies.³¹⁻³⁵ 15

included patients with lower extremity diabetic ulcers,^{10, 11, 14, 16-24, 28, 29, 32} 11 included patients with lower extremity venous ulcers,^{12, 13, 15, 20, 25-27, 30, 31, 34, 35} and 2 included patients with pressure ulcers in any location.^{33, 36} Length of followup after treatment ranged from none to 11 months.

KQ 1: Comparative effectiveness of platelet-rich plasma

Lower extremity diabetic ulcers

Fourteen RCTs^{10, 11, 14, 16-24, 28, 29} and 1 comparative observational study³² with 1,096 patients evaluated autologous platelet-rich plasma (PRP) in lower extremity diabetic ulcers. On average, these patients were 58.25 years old (range: 40.10 to 70.24); 37 percent were female; and 73 percent were Caucasian. The average initial wound size varied greatly from 0.02 cm² to 28.40 cm², though most of the wound size ranged between 2 cm² and 4 cm². Most of the studies included only lower grade wounds, but a few studies included severe wounds (Grade 4 and above). Two studies reported a run-in period ranging from 1 week to 4 weeks.^{10, 23} The length of followup after intervention ranged from no followup to 11 months with a median of 6 weeks. 10 studies (66.67%) reported a minimum 1 month chronicity of the target ulcer before starting the PRP treatments. Two studies indicated that, as the ulcers were presumed to be recurrent, they did not specify a minimum duration of ulcer formation.^{18, 21} The risk of bias was judged to be high in 8 RCTs (57.14%), moderate in 6 RCTs (42.86%) and high in the one observational study (100%).

Compared with management without PRP, autologous PRP demonstrated a statistically significant increase in complete wound closure or healing (Relative risk [RR]: 1.20; 95% CI: 1.09 to 1.32; Moderate strength of evidence [SOE]). SOE was lowered from high to moderate because of risk of bias, and because of not having concerns about other domains of SOE. PRP also shortened time to complete wound closure (range: -40 to -4.90 days; Low SOE), and reduced wound area and depth (Low SOE). Medicare-eligible older adults were underrepresented in the included studies. Evidence was insufficient to estimate an effect on important outcomes such as pain, hospitalization, amputations and wound recurrence. There was no statistically significant difference in adverse events (AEs) and serious adverse events (SAEs) between PRP and management without PRP.

Lower extremity venous ulcers

Eight RCTs^{12, 13, 15, 20, 25-27, 30} and 3 observational studies^{31, 34, 35} with 615 patients evaluated PRP in lower extremity venous ulcers. Seven RCTs^{12, 13, 15, 20, 25, 27, 30} and 3 comparative observational studies^{31, 34, 35} compared PRP to management without PRP. One RCT evaluated PRP in patients after skin grafting procedure.²⁰ Another RCT compared autologous platelet lysate to placebo buffer solution in 86 patients with venous leg ulcers.²⁶ On average, these patients were 61.13 years old (range: 32.50 to 76.80); and 49.10 percent were female. The patients had their index venous ulcer for at least 6 weeks (range: 6 weeks to 8.50 years). The average initial wound size varied considerably from 2.90 cm² to 18.10 cm². Only 1 study reported a two-week run-in time.¹⁵ All but two study reported less than 4 weeks' length of followup.^{20, 27} The overall risk of bias was moderate in the RCTs and high in the observational studies.

Evidence was insufficient to estimate an effect of autologous platelet-rich plasma or autologous platelet lysate on the outcome of complete wound closure or time to complete wound

closure in patients with lower extremity venous ulcers. There was no statistically significant difference in AEs between PRP and management without PRP.

Pressure ulcers

One RCT²⁹ and one comparative observational study³³ evaluated PRP in pressure ulcer. The average age of these patients was 57.64 years old; 41 percent were female. Mean duration of pressure ulcers was 72.80 days. Ulcers treated by PRP included Grade 2 (54.55%) and 4 (45.45%); while ulcers treated by management without PRP included Grade 2 (74.54%), 3 (7.27%) and 4 (18.18%) The length of followup after intervention was none to at least 6 months.^{33, 36} The overall risk of bias was moderate in the RCT and high in the observational studies.

No studies evaluated the outcome of complete wound closure. Evidence was insufficient to estimate an effect of autologous platelet-rich plasma on wound area in patients with pressure ulcers.

KQ 2: Types of platelet-rich plasma preparations currently being marketed in US

Food and Drug Administration (FDA) has not licensed any PRP products for any specific indications. If a medical device is labeled or promoted for manufacturing PRP for the purpose of administering the device output to a patient, then the device would require FDA approval or clearance for that use prior to marketing in the United States. A physician may use a cleared or approved medical device for the treatment of a particular patient in a manner that differs from the cleared or approved indication (known as off-label use).

FDA has cleared medical devices that are indicated to prepare autologous PRP at the patient's point of care. PRP preparations currently marketed in US medical practices are in 2 forms: autologous PRP in aqueous form for application with dressing or injection to the wound bed, or the gel form for application to the wound bed. The gel form can be produced from adding thrombin with or without calcium chloride to the PRP, or by centrifuging whole blood without anticoagulant at low speed. Of each form, leukocyte count could be different depending on the provider's preference.

KQ3: Platelet-rich plasma preparations currently being investigated in ongoing trials

We identified 22 ongoing trials from trial registries.³⁷⁻⁵⁸ Six trials are being conducted investigating PRP therapy in lower extremity venous ulcers,^{39, 42-44, 47, 52} 12 studies in lower extremity diabetic ulcers,^{37, 38, 40, 41, 45, 46, 49, 50, 54, 56-58} and 3 studies in pressure ulcers at any location.^{48, 53, 55} One study plans to investigate PRP treatment for a mixed variety of ulcers at any location.⁵¹ These clinical trials showed a variety of PRP preparation methods, applications for wound care, treatment duration, and followup period.

KQ4: Best practices in study design

For all three types of wounds, rigorous studies are needed. RCTs need to be protected from selection bias with adequate allocation concealment and should have blinded outcome assessment. Prospective observational studies are also needed, but with clear stratification or adjustment for important prognostic variables (wound duration, patient age and comorbidities

including diabetes control, arterial flow status with appropriate measurement, and venous insufficiency) as well as for co-interventions (e.g., debridement and offloading).

Future studies should focus on the characterization of the PRP products, with clear description of platelet concentration, key growth factor content, and leukocyte count. Detailed data on potential confounders such as body mass index, appropriately measured arterial perfusion, smoking status, occupation pertinent to weight bearing, and nutrition status should be collected and used when possible to stratify the results to allow better patient selection. Detailed description of the comparison group needs to be explicitly stated in future studies and conform to best practices in wound management. Outcomes, such as standardized wound classification, complete wound closure, quality of life, psychological distress measures, and wound recurrence, need to be evaluated. Sample size calculations should be based on the baseline risk of these patient important outcomes, as opposed to power analysis based on changes in wound size. Long-term followup would be needed to examine the durability of the therapeutic effect. A 21 item checklist developed by the International Working Group of the Diabetic Foot (IWGDF) may be used to plan and report studies in diabetic foot ulcers.⁵⁹ In addition, studies using “big data” may also be useful to identify responsive population and provide guidance on life style modification that is critical for the success of the therapy.

KQ5: Evidence gaps

We found a very small number of studies evaluating autologous PRP in three chronic wound etiologies. Data were particularly limited for lower extremity venous ulcers and pressure ulcers and the evidence to support PRP use in these two etiologies is insufficient. Although the three types of wounds studied share common pathophysiologic processes (local tissue hypoxia, bacterial colonization and an inflammatory environment⁶⁰), extrapolation of efficacy across wound type would be challenging.

For venous and pressure ulcers, we simply need more studies. For lower extremity diabetic ulcers, evidence for effectiveness is available for wound healing outcomes; however, data are needed on the outcomes of amputation, infection, and hospitalization.

Discussion

Overview

This systematic review evaluated the effectiveness and safety of platelet-rich plasma (PRP) for chronic wounds including lower extremity diabetic ulcers (14 randomized controlled trials [RCTs] and 1 observational study), lower extremity venous ulcers (7 RCTs and 3 observational study), and pressure ulcers (2 observational study). In addition, 1 RCT evaluated autologous platelet lysate in patients with venous ulcers. Effectiveness and safety were assessed according to wound type.

Diabetic ulcers have been studied the most. PRP therapy increases the proportion of completely closed or healed lower extremity diabetic ulcers (moderate strength of evidence [SOE]), shortens the time to complete wound closure (low SOE), and reduces wound area and depth (low SOE), compared with management without PRP. No significant changes were found in terms of wound infection, amputation, wound recurrence, or hospitalization. In patients with lower extremity venous ulcers, for critical outcomes, such as complete wound closure or time to

complete wound closure, the evidence was insufficient and the estimates were statistically nonsignificant. Similarly, evidence was insufficient to estimate an effect on any outcome in pressure ulcers.

In terms of safety, there was no clear signal of harm for all three wound types. There was no statistically significant difference in death, total adverse events (AEs) or serious adverse events (SAEs) between PRP and management without PRP. These data were primarily from the studies of lower extremity diabetic ulcers; with much less AE data in venous and pressure ulcers. From clinical perspective, patients and clinicians would be concerned about dermatologic, hematologic, neurologic, and rheumatologic AE. These were not statistically significantly different between PRP and management without PRP; although these analyses are clearly underpowered.

Limitations

We were unable to identify ideal patient characteristics to initiate, continue, or discontinue PRP. Our findings were limited by lack of standard reporting of the following: 1) PRP formulation techniques (centrifuge type, centrifuge speed, centrifuge time, radius of rotor); 2) PRP concentration, formulation and volume used; 3) lower extremity diabetic ulcer offloading procedures and periprocedural restrictions; and 4) patient recruitment methods including underrepresentation of older adults, followup procedures and run-in periods. Our findings are based on studies that differ from a real world Medicare population, particularly not including older patients. In addition, qualitative and quantitative syntheses were restricted by heterogeneity of the included studies, in terms of patient population, inclusion/exclusion criteria, wound severity, use of PRP (formulation, application techniques, frequency, dosage, duration of treatment), outcome assessment, length of followup, and study design. The evaluation of adverse events was also limited by the fact that 39% of the included studies (9/23) did not evaluate adverse events and majority of the rest did not use a consistent approach for reporting and evaluation. We could not statistically evaluate publication bias in almost all of the comparisons because the number of studies included in these comparison was small ($n < 10$). We judged the included studies to have moderate to high risk of bias because of potential deviations from intended interventions, missing outcome data, bias from randomization process, lack of comparability between study groups and lack of independent blind assessment of outcomes. Finally, failure to detect statistical significance for many of the outcomes could have resulted from small sample sizes and lack of power.

Implications and Conclusions

In individuals with lower extremity diabetic ulcers, autologous platelet-rich plasma increases complete wound closure (moderate SOE), shortens healing time (low SOE) and reduces wound size (low SOE). The evidence is insufficient to estimate an effect of autologous platelet-rich plasma on wound healing in individuals with venous ulcers or pressure ulcers.

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Introduction

Background

Chronic wounds are a common chronic medical condition with a high impact on the aging population, with chronic wounds or infections affecting nearly 15 percent of Medicare beneficiaries with a healthcare burden of \$28 to \$96 billion United States (US) dollars per year.¹ Conditions that are most commonly associated with wound formation include diabetes, pressure injuries, and venous or arterial diseases. Normal wound healing involves a complex process characterized by orderly and sequential events resulting in the restoration of tissue integrity and function.² The cascade of events starts from hemostasis, followed by inflammation, cell recruitment, migration, proliferation, tissue modeling and remodeling. Cytokines and growth factors play a key regulatory role.³ Wound healing is further complicated by location, depth, size, and microbial contaminations. Aberrations of wound healing are associated with advanced age, certain medical comorbidities, and genetic predisposition. Non-healing wounds develop when wounds fail to progress in a timely sequence of events often due to more than one of the above factors. Chronic non-healing wounds often necessitate costly long-term wound management and result in significant discomfort and frustration to patients.

Current treatment modalities focus on treatment of underlying disorders and good wound care to promote healthy granulation tissue.⁴ For diabetic foot ulcers, this involves restoring perfusion, offloading pressure, wound debridement, treating infection, optimal glycemic control and good wound care. For venous ulcers, compression, debridement, treatment of venous reflux, and good wound care are important. For pressure ulcers, management of pressure, friction, shear and moisture in addition to good wound care are critical. New treatment modalities aimed at optimizing the microenvironment in addition to standard of care with application of growth factors such as platelet-derived growth factor (PDGF), so that the healing process of chronic wound may be induced or accelerated.⁵

Autologous platelet-rich plasma (PRP) is the fraction of blood plasma from a patient's peripheral blood that contains higher than baseline concentrations of platelets including concentrated growth factors and cytokines. PRP contains PDGF, Fibroblast Growth Factor (FGF), Insulin Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor- β (TGF- β), and Hepatocyte Growth Factor (HGF), all of which have been all shown to stimulate healing.⁶ The contents of the platelet in PRP are either released through spontaneous activation upon exposure to collagen in the wounds,⁷ pre-released as PRP lysate by freeze-thawing disruption of platelet membrane,⁸ or pre-released by activation with degranulation triggered by thrombin and/or calcium chloride.⁹ PRP has attracted significant interest because platelets possess various growth factors that are critical for tissue repair and regeneration, and they have antibacterial properties in traumatic injuries.^{10,11}

PRP preparations are being offered typically in a point-of-care setting, delivered as a preparation of aqueous suspension obtained by centrifugation of whole blood or as a gel. PRP is most commonly applied to the wound bed with dressing, but can be injected in the wound bed. PRP contains concentrated platelets, as few red blood cells as possible, and leukocytes at different levels for various indications. Leukocyte-rich PRP is commonly used in wound care for leukocyte's role in local cleaning and immune regulation of the wound healing process.^{12,13} Variability of PRP contents secondary to preparation technology and individual difference poses a challenge for research.¹⁴

In summary, this systematic review evaluates the overall effectiveness of treatment of lower extremity diabetic ulcers, lower extremity venous ulcers, and pressure ulcers with PRP, as well as the impact of PRP content, carriers, dosage, frequency and duration of application.

Key Questions

The following Key Questions (KQs) were determined based on input from multiple key informants, and the public (drafted KQs were posted for public comment between June 23rd and July 22nd, 2020). The related PICOTS (population, interventions, comparisons, outcomes, timing, and setting) are listed in Table 1.

Comparative Effectiveness Questions:

KQ1. What are the benefits and harms of treatment strategies including PRP alone with or without other wound care treatments compared with other wound care treatments in patients with diabetic, venous and pressure chronic wounds, for patient oriented outcomes such as at least the following: completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements), time to complete wound closure, wound reoccurrence, risk of developing wound infection, amputation, hospitalization (frequency and duration), return to baseline activities and function, reduction of wound size, pain, opioid medication use, exudate and odor, quality of life and adverse effects?

KQ 1.a. Describe the risk of bias in the studies examined by chronic wound type and study design.

KQ 1.b. What are the differences in formulation techniques and components between these preparations? What are the differences in application techniques, frequency of application and “dosage” (amounts applied)?

KQ 1.c. What are the study characteristics (such as those listed below) in each included investigation for each chronic wound type treated by PRP?

- i. Comparator (if standard care, describe in detail).
- ii. Study inclusion/exclusion criteria and patient characteristics of enrollees, including at least age, gender, and general health (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal), wound characteristics, and prior and concurrent wound treatments.
- iii. Wound characteristics of enrollees including at least wound type, wound size/depth/duration/severity, vascular status, infection status and whether there were inter- and intra-rater checks of wound measurements.
- iv. Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period.
- v. Definition of wound characteristics: definition of “failure to heal”, and definition of a successfully healed wound (re-epithelialization).
- vi. Method of applying skin PRP including provider, frequency of application, definition of standard of care, and handling of infections.
- vii. Measurement and assessment methods including method of assessment(s); frequency and time points for assessment(s)

(including long-term assessments for durability of heal); and blinding of assessors.

- KQ 1.d. Based on the included studies, what are the patient characteristics commonly considered for the initiation and continuation/discontinuation of PRP in patients with chronic wounds?

Contextual Questions:

- KQ2. What types of PRP preparations are currently being marketed in US medical practices (gel, liquid, etc.)?
KQ3. What PRP preparations are currently being investigated in ongoing trials?

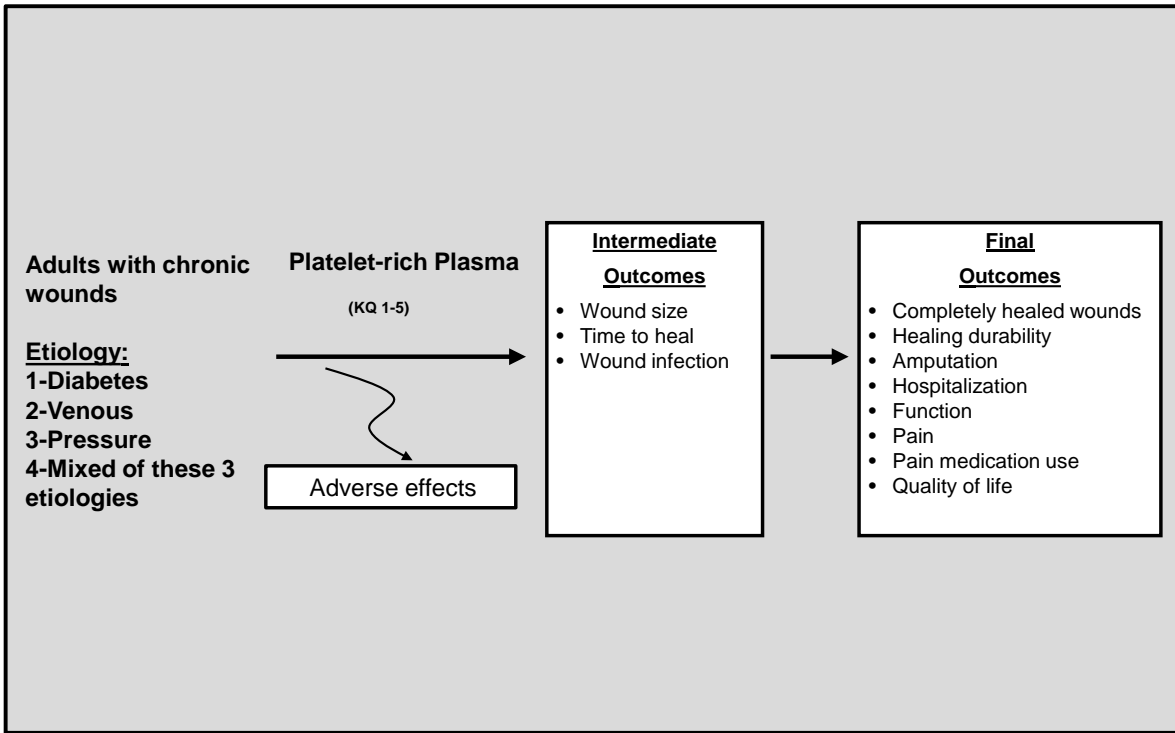
Future Research Questions:

- KQ4. What best practices in study design could be used to produce high quality evidence on PRP?
KQ5. What are the evidence gaps found in this body of research?

Methods

We developed an analytic framework to guide the process of the systematic review (Figure 1). We followed the established methodologies of systematic reviews as outlined in Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews.¹⁵ The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.¹⁶ The study protocol is published on AHRQ website (<https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/platelet-rich-plasma-protocol-amendment.pdf>) and registered in the international prospective register of systematic reviews (PROSPERO #: CRD42020172817).

Figure 1. Analytic Framework for Key Questions



KQ= key question

1. Literature Search Strategy

a. Search Strategy

We conducted a comprehensive search of bibliographic 8 databases, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to June 11, 2020. We searched Food and Drug Administration (FDA) website, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ’s Horizon Scanning System, the International Working Group on the Diabetic Foot (IWGDF) website, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant original studies, relevant systematic reviews and meta-analysis to identify additional existing and new literature was conducted. The search strategy was developed an experienced medical librarian and peer-reviewed by an independent information specialist. The same medical librarian conducted the search. The detailed search strategy is listed in Appendix B.

2. Inclusion and Exclusion Criteria

The eligible studies had to meet all of the following criteria: 1) adult patients (18 years and older) with lower extremity diabetic ulcers, lower extremity venous ulcers, pressure ulcers, or

mixed of these three etiologies; 2) received autologous platelet-rich plasma or autologous platelet lysate; 3) compared with any other wound care without platelet-rich plasma or autologous platelet lysate; 4) reported outcomes of interest; 5) randomized controlled trials (RCTs) and comparative observational studies; and 6) published in English. We excluded wounds of other etiologies, including traumatic wounds, peripheral arterial disease (PAD) related wounds in non-diabetics (i.e., diabetic wounds are to be included regardless of the presence of PAD, but PAD alone wounds without diabetes are a reason of exclusion), and acute wounds (<4 weeks). We also excluded studies with mixed, non-stratified etiologies other than diabetic, venous or pressure wounds. In vitro studies, studies without original data (e.g., narrative review, editorial, secondary analyses of published trials, single-arm studies), and studies published in non-English languages were also excluded. The detailed inclusion and exclusion criteria are listed in Table 1.

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	Adult patients (18 years and older) with Lower extremity diabetic ulcers Lower extremity venous ulcers Pressure ulcers in any location Mixed of these 3 etiologies	Animals Children (age < 18 years) Wounds of other etiologies Studies with mixed (other etiologies), non stratified etiologies other than diabetic, venous or pressure wounds. Traumatic wounds PAD related wounds in non-diabetics (i.e., diabetic wounds are to be included regardless of the presence of PAD, but PAD alone wounds without diabetes are a reason of exclusion). Wounds<4 weeks
Intervention	Any preparation of autologous platelet-rich plasma, or autologous platelet lysate	Allogeneic PRP
Comparators	Any other wound care without platelet-rich plasma, or autologous platelet lysate	None
Outcomes	Completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements versus failure to heal) Time to complete wound closure Healing durability (Time to wound reoccurrence) Wound infection (improvement of wound infection or reduced risk of developing wound infection) Amputation Hospitalization Return to baseline activities of daily living and function Wound size Pain Opioid medication use Quality of life Adverse effects	None
Timing	Any	None
Settings	Any	None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Study design	KQ 1 Original data Any sample size RCTs Comparative observational studies Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	<i>In vitro</i> studies, non-original data (e.g. narrative reviews, editorials, letters, or erratum), single-arm observational studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., non-longitudinal) studies, before-after studies that do not have a comparison group, survey
Subgroup analysis	Age Gender Comorbidities (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal disease, liver disease) Wound characteristics (wound type, area, depth, volume, duration, severity, vascular status, infection status, and prior and concurrent wound treatments) Anatomical location (lower extremity diabetic ulcers only) PRP formulation techniques PRP components PRP application techniques PRP frequency PRP “dosage” (amounts applied) PRP offloading procedures (e.g., total contact casting, removable CAM Walker™, irremovable offloading devices) Use of immunosuppressant medication Nutrition status Pain medication (opioids, others) Length of follow-up Settings Control group (standard care vs. non-standard care)	
Publications	Studies published in English only.	Non-English language studies

KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PAD=peripheral arterial disease; PRP = platelet-rich plasma; RCT = randomized controlled trial

3. Study Selection

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus.

4. Data Abstraction and Data Management

We developed a standardized data extraction form to extract study characteristics (author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form was tested by all study team members using randomly selected 10 studies. Reviewers worked independently to extract study details. A second reviewer reviewed data

extraction, and resolved conflicts. When the included studies did not report all necessary information (e.g., methods and results), we contacted authors directly.

5. Assessment of the Risk of Bias of Individual Studies

We evaluated the risk of bias of the included RCTs using the Cochrane Collaboration’s Risk of Bias 2 tool¹⁷ to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For observational studies, we selected appropriate items from the Newcastle-Ottawa Scale.¹⁸ The overall risk of bias for a study was rated as low risk when all of the above domains were judged to be low risk; moderate when at least one domain was rated as moderate and no domain as high; and high risk when at least one domain was rated as high risk.

6. Data Synthesis

We qualitatively summarized key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

Table 2 lists the categories of adverse events and examples. Infection and amputation were treated as effectiveness outcomes in this report. We used the definition of serious adverse events listed by the original studies.

Table 2. Categories of adverse events

Type of Adverse Events	Example
Dermatological Adverse event	Dermatitis, maceration, perilesional itch, burning sensation, exudation
Endocrine Adverse Event	Hypoglycemia
Gastrointestinal Adverse Event	Nausea, vomiting
Hematologic Adverse Event	Anemia, thrombophlebitis
Neurological Adverse Event	Pain, stinging, confusion
Respiratory Adverse Event	Upper respiratory infection, pneumonia
Rheumatology Adverse Event	Allergic rash
Other Adverse Event	General malaise

Analyses were based on intention-to-treat (ITT) principle for RCTs or number of patients initially assigned to the treatments at the start of the study for observational studies. We conducted meta-analysis, whenever appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures), to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. Studies that randomized wounds, instead of patients, were qualitatively synthesized as we were unable to control correlations between wounds within a patient. We extracted or calculated relative risk (RR) and corresponding 95 percent confidence intervals for binary outcomes. For continuous outcomes, we calculated weighted mean difference (WMD), measuring mean difference between the intervention and the comparison, as the included studies used the same outcome measure. For adverse events (except mortality), we calculated rate ratio (i.e. ratio of the incidence rate of events within a given time between the intervention and the comparison). We used the DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 3.¹⁹ The fixed effect method based on the Mantel and Haenszel method was adopted when the number of studies is 3 or less. We evaluated heterogeneity

between studies using the I^2 indicator. To further explore heterogeneity, we conducted pre-specified subgroup analyses based on length of follow-up, study settings, comorbidity (peripheral arterial disease), smoking, antibiotics use, PRP activation, PRP formulation, administration route, and leukocyte counts. We conducted sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias. We used funnel plot and Egger's regression test to statistically evaluate publication bias when the number of studies included in a meta-analysis is not less than 10 ($n \geq 10$).

7. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We graded the strength of the body of evidence (SOE) following the Evidence-based Practice Center (EPC) methods guide on assessing SOE.¹⁵

RCTs started as high SOE.¹⁵ The domains used for all KQs were: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We lowered SOE grading for the risk of bias when all the studies in a particular comparison had high or unclear risk of bias. If estimates from high and low risk of bias studies were available and were similar, we combined them and did not rate down SOE. If estimates were different, we only used the low risk of bias estimate and did not rate down SOE (although this could lead to imprecise estimates). In this systematic review, none of the studies had low risk of bias. There were some with moderate and some with high ratings. Analyzing them separately did not make a difference in the estimated effect. Hence, the whole body of evidence (SOE) was graded down one level due to risk of bias. We rated down for imprecision when the number of events was small (<300) or the confidence intervals included substantial benefits and harms (defined as 0.25 relative risk reduction or increase). We rated down for inconsistency when the I^2 exceeded an arbitrary cutoff >60 percent and visual inspection of forest plots suggested substantial variability in point estimates.

Based on this assessment and the initial study design, we assigned SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect'.

High - We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).

Moderate - We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).

Low - We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient - We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

We produced summary of evidence tables that provided for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

8. Assessing Applicability

We followed the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.¹⁵ Applicability for each outcome was summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. The following factors that may affect applicability have been identified, including patient factors (e.g., demographic characteristics (age, race, ethnicity, gender, socioeconomic status [SES]), patient medical comorbidities (e.g., diabetic control, body mass index [BMI]), intervention factors (e.g., dose/frequency of treatment, type of treatment, and treatment duration), comparisons (e.g., type of comparators), outcomes (e.g., use of unvalidated or non-standardized outcomes), settings, and study design features (e.g., observational studies, RCTs). We used this information to evaluate applicability of the evidence to real-world clinical practice in typical U.S. settings. We reported any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

9. Peer Review and Public Commentary

A draft report was posted for peer review and public comments between June 23rd and July 22nd, 2020. We revised and finalized the draft report in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Literature Searches and Evidence Base

The literature search identified 4,147 citations. An additional 172 references were identified through reference mining, grey literature search; and from Technical Experts. There were 27 studies and 1,796 patients included in the systematic review (Appendix Figure A.1.). Of the 27 studies, 22 were randomized controlled trials (RCTs)²⁰⁻⁴¹ and 5 were comparative observational studies.⁴²⁻⁴⁶ 15 included patients with lower extremity diabetic ulcers,^{20, 21, 24, 26-33, 37, 39, 41, 43} 11 included patients with lower extremity venous ulcers,^{22, 23, 25, 30, 34-36, 40, 42, 45, 46} and 2 included patients with pressure ulcers in any location.^{38, 44} 5 studies were conducted in Africa,^{26, 27, 36, 37, 42} 9 in Asia,^{20, 22, 28, 31, 33, 38-40, 44} 10 in Europe,^{23, 25, 29, 30, 32, 34, 41, 43, 45, 46} 1 in Australia,³⁵ and two were in the United States.^{21, 24} Length of follow-up after intervention ranged from none to 11 months.

A list of the studies excluded at the full-text review stage is in Appendix C.

Key Question 1. What are the benefits and harms of treatment strategies including platelet-rich plasma (PRP) alone with or without other wound care treatments compared with other wound care treatments in patients with diabetic, venous and pressure chronic wounds, for patient oriented outcomes such as at least the following: completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing

requirements), time to complete wound closure, wound reoccurrence, risk of developing wound infection, amputation, hospitalization (frequency and duration), return to baseline activities and function, reduction of wound size, pain, opioid medication use, exudate and odor, quality of life and adverse effects?

Lower Extremity Diabetic Ulcers

Key points

- PRP increased the proportion of completely healed lower extremity diabetic ulcers (Moderate strength of evidence [SOE]), shortened time to complete wound closure (Low SOE), and reduced wound area and depth (Low SOE), compared with management without PRP, although Medicare-eligible older adults were underrepresented in the included studies.
- Evidence was insufficient to estimate an effect on important outcomes such as pain, hospitalization, amputations and wound recurrence.
- There was no significant difference on adverse events (AEs) and serious adverse events between PRP and management without PRP.

Study characteristics

Fourteen RCTs^{20, 21, 24, 26-33, 37, 39, 41} and 1 comparative observational study⁴³ with 1,096 patients evaluated autologous PRP in lower extremity diabetic ulcers. One RCT evaluated PRP in patients after skin grafting procedure and was analyzed separately.³⁰ Appendix Tables D.1., E.1., F.1., and H.1. list the study characteristics. On average, these patients were 58.25 years old (range: 40.10 to 70.24); 37 percent were female; and 73 percent were Caucasian. 11 to 34 percent of the patients had chronic kidney disease; 33 percent to 92 percent had hypertension; 8 percent to 40 percent coronary heart disease, 29 percent to 80 percent had hyperlipidemia; 33 percent to 60 percent were overweight or obese; 8 percent to 58 percent were smokers; and 39 percent to 78 percent had peripheral arterial disease. Most of the studies did not specify how they identified and recruited patients. Two studies recruited patients through referral. The length of follow-up after intervention ranged from no followup to 11 months with a median of 6 weeks. 10 studies (66.67%) reported a minimum 1 month chronicity of the target ulcer before starting the PRP treatments. Two studies indicated that as the ulcers were presumed to be recurrent they did not specify a minimum duration of ulcer formation.^{28 31}

The average initial wound size varied greatly from 0.02 cm² to 28.40 cm², though most of the wound size ranged between 2 cm² and 4 cm². Most of the studies included only lower grade wounds, but a few studies included severe wounds (Grade 4 and above).

Studies reported different levels of details on methods used in wound measurement (Appendix Table I.1.). These methods included photo documentation, clock method, and wound tracing. Ultrasound probe or measuring tape were used. One study used the Bates Jensen Wound Assessment Tool to assess wounds.³³ Bi-weekly or weekly assessment was the common frequency for wound assessment. No study reported using inter-rater or intra-rater checks. 6

studies reported blinding of wound assessors.^{20, 21, 24, 29, 32, 41} Two studies reported a run-in period ranging from 1 week to 4 weeks.^{20, 41}

Management without PRP

Management without PRP, the control groups reported by the included studies, included simple saline dressings,^{31, 37, 39} proprietary saline gel,²¹ hydrocolloid dressing,⁴³ polyurethane foam dressings, hydrogels, alginates along with water-solubility hydrocolloids-kolloidnye bandage,^{22, 32} saline and Vaseline gauze dressing,⁴² and skin graft.³⁰ In addition, a study used platelet poor plasma as a control intervention.²⁷ The use of systemic antibiotics was reported in 3 studies.^{28, 30, 33} Offloading was explicitly described in one study.⁴¹ Only two studies referred to professional or societal guidelines for usual and conservative care.^{24, 41} Four studies did not clearly define what they referred to as “usual care” or “standard care”.^{28-30, 33}

PRP formulation techniques and components, application techniques, frequency of application and “dosage”

Among the 15 studies (14 RCTs and 1 observational study) investigating PRP for treatment of lower extremity diabetic ulcers, formulation technique was highly variable in terms of what was reported and when this information was reported in terms of number of centrifuge spins. Eleven studies used a gel formulation for PRP application.^{20, 24, 26, 27, 28-30, 37, 39, 41} One study mixed PRP with thrombin and calcium gluconate and applied PRP to the wound bed via pipette,²⁰ others prepared PRP for application via dressing,^{31, 37, 43} another applied PRP via injection to the wound bed,³³ and one study delivered gel prepared with a proprietary gravitational separation system.³² In terms of dosage, studies prepared PRP from whole blood varying in volume from up to 20 ml,^{21, 24, 26, 33, 43} others 20-100 ml,²⁰ 30 ml,³¹ 15 ml,³⁰ 10 ml,^{27, 28} and at least 55 ml.³² In terms of frequency, most studies provided biweekly treatments^{21, 26-28} (once or twice weekly),²⁴ or weekly treatments,^{29, 30, 32, 33, 41} every 10 days,⁴³ every two days,³¹ or every three days.²⁰ Total treatment duration varied as well, with many studies reporting treatment of 12 weeks^{20, 21} (up to 20 weeks),²⁴ 3 months,²⁶ one month,^{28, 30, 43} up to 20 weeks,^{27, 37, 41} 8 weeks,³² 5 weeks,²⁹ or 3 weeks.³¹ Total dosage was not calculated for any study but rather was defined by volume, frequency, and total duration of treatment.

Risk of bias

The risk of bias was judged to be high in 8 RCTs (57.14%), moderate in 6 RCTs (42.86%) and high in the one observational study (100%) (Appendix Tables G.1. and G.2.). We were only able to statistically evaluate publication bias for one outcome, complete wound closure, and found no indication for publication bias (p=0.08).

PRP effectiveness and adverse events

Table 3 lists the effectiveness of PRP when compared with management without PRP. Compared with management without PRP, PRP was associated with statistically significantly more complete wound closure (Appendix Figure Q.1.1.), shorter time to complete wound closure, more wound area and wound depth reduction. No significant difference was found on number of amputation (Appendix Figure Q.1.2.), hospitalization, pain reduction, wound infection (Appendix Figure Q.1.3.), and wound recurrence. There was no significant difference on total number of adverse events, number of withdrawals, and number of withdrawals due to adverse events (Appendix Table K.1.). Two RCTs reported a total of 51 non-treatment-related serious

AE from 46 patients in the PRP group, including 4 deaths. There was no statistically significant difference between PRP and management without PRP in number of serious AEs and number of death.

One RCT³⁰ compared PRP plus standard care to standard care after skin grafting procedure. There was no statistically significant difference on complete wound closure between the two groups (RR= 1.09, 95% CI: 0.66 to 1.82).

Appendix Table J.1. summarizes the findings by individual studies.

Table 3. Comparison of PRP versus management without PRP for lower extremity diabetic ulcers

Comparison	Outcome	Findings	Study Design, number of patients	Strength of evidence (rationale)
PRP vs. Management without PRP	Complete wound closure	RR: 1.20; 95% CI: 1.09 to 1.32; I ² =0.00%	12 RCTs; ^{20, 24, 26, 21, 27, 29, 31-33, 37, 39, 41} 890 patients	Moderate (risk of bias)
		HR: 1.71, 95% CI: 1.07 to 2.73; I ² =N/A	1 RCT; ⁴¹ 269 patients	
	Time to complete wound closure	Meta-analysis not feasible WMD: -4.90 days, p=0.001 ²⁸ WMD: -23.90 days, p<0.001 ³³ WMD: -40 days, p=0.13 ²¹ WMD: -12 days, p=0.03	4 RCTs; ^{21, 28, 33, 41} 189 patients	Low (risk of bias and imprecision)
	Hospitalization	RR: 0.51; 95% CI: 0.20 to 1.34; I ² =0.00%	2 RCTs; ^{21, 24} 201 patients	Insufficient (risk of bias, severe imprecision)
	Amputation	RR: 0.89; 95% CI: 0.43 to 1.84; I ² =0.00%	4 RCTs; ^{24, 31, 33, 41} and 1 comparative observational; ⁴³ 613 patients	Insufficient (risk of bias, severe imprecision)
	Wound infection	RR: 0.77; 95% CI: 0.54 to 1.11; I ² =3.00%	7 RCTs; ^{21, 24, 26, 28, 31, 33, 41} 717 patients	Insufficient (risk of bias, severe imprecision)
	Pain scale (visual analog scale)	WMD: -1.10; 95% CI: -1.81 to -0.39; I ² =N/A	1 RCT; ²⁸ 76 patients	Insufficient (risk of bias, severe imprecision)
		% change: -54.5% vs. -45.5%, p=0.12	1 RCT; ⁴¹ 269 patients	
	Wound recurrence	RR: 2.09.; 95% CI: 0.31 to 13.93; I ² =0.00%	2 RCTs; ^{21, 24} 201 patients	Insufficient (risk of bias, severe imprecision)

Comparison	Outcome	Findings	Study Design, number of patients	Strength of evidence (rationale)
	Wound area (cm ²)	WMD: -0.11; 95% CI: -0.15 to -0.06; I ² =77.40%	3 RCTs; ^{29, 31, 41} 343 patients	Low (risk of bias and imprecision)
	Wound depth (cm)	WMD: -0.85; 95% CI: -1.39 to -0.30; I ² =N/A	1 RCT; ³¹ 60 patients	Low (risk of bias and imprecision)

CI = confidence interval; cm = centimeter; HR = hazard ratio; N/A = not applicable; PRP = platelet-rich plasma; RCT = randomized controlled trial; RR= risk ratio; WMD = weight mean difference

Subgroup analysis

When PRP compared with management without PRP, activated PRP was associated with significantly more reduction of wound area than non-activated PRP (activated PRP: -1.85 cm²; 95% CI: -3.03 to -0.67 vs. non-activated PRP: -0.10 cm²; 95% CI: -0.15 to -0.06). Subgroup analysis based on length of followup (<6 weeks vs. ≥6 weeks), settings (inpatient vs. outpatient), peripheral arterial disease, smoking, use of antibiotics, PRP formulation, administration route, and leukocyte counts showed no significant difference when PRP compared with management without PRP (Appendix Table P.1.). A subgroup analysis of the control groups did not find significant difference between standard care and non-standard care.

Sensitivity analysis

Sensitivity analyses by excluding studies with high risk of bias did not show significant differences on outcomes (Appendix Table O. 1.).

Lower Extremity Venous Ulcers

Key points

- Evidence was insufficient to estimate an effect of PRP on the outcome of complete wound closure or time to complete wound closure in patients with lower extremity venous ulcers.
- Evidence was insufficient to estimate an effect of autologous platelet lysate on complete wound closure in patients with lower extremity venous ulcers.
- There was no significant difference on adverse events between PRP and management without PRP.

Study characteristics

Eight RCTs^{22, 23, 25, 30, 34-36, 40} and 3 observational studies^{42, 45, 46} with 615 patients evaluated PRP in lower extremity venous ulcers. Seven RCTs^{22, 23, 25, 30, 34, 36, 40} and 3 comparative observational studies^{42, 45, 46} compared PRP to management without PRP. One RCT evaluated PRP in patients after skin grafting procedure and was analyzed separately.³⁰ Another RCT compared autologous platelet lysate to placebo buffer solution in 86 patients with venous leg ulcers.³⁵ One study compared PRP to zinc oxide paste.⁴⁰ Appendix Tables D.2., E.2, F.2., and H.2. list the study characteristics. On average, these patients were 61.13 years old (range: 32.50 to 76.80); and 49.10 percent were female. Thirty-two percent of the patients had chronic kidney disease, 12 percent had coronary heart disease, 47 percent arterial hypertension, 3 percent to 17 percent diabetes, and 33 percent to 85 percent were smokers. The average body mass index (BMI) reported by the studies ranged from 21.00 to 29.10. Most of the studies did not specify

how they identified and recruited patients. One study identified all eligible patients attending the leg ulcer clinic.³⁵ One study recruited patients from a department of dermatology, venereology and leprosy.⁴⁰ One study reported a two-week run-in time.²⁵ All but two studies reported less than 4 weeks' length of followup.^{30, 36} The patients had their index venous ulcer for at least 6 weeks (range: 6 weeks to 8.5 years). The average initial wound size varied considerably from 2.90 cm² to 18.10 cm².

Studies reported various details of methods used in measuring wounds (Appendix Table I.2.). These methods included photo documentation, clock method, and wound tracing. Ultrasound probe or measuring scale was used. To calculate wound area, the Kundin method (i.e., Area = Length x Width x 0.785) was often reported. Weekly assessment throughout the study period was the most common frequency for wound assessment. Only two studies reported using inter-rater or intra-rater checks.^{23, 34} One study reported blinding of wound assessors.³⁶

Management without PRP

All the included studies reported the use of a wound dressing that varied from simple wet to dry to more modern dressings that were used in the remaining studies. These modern dressings were described to emphasize a moist wound environment and minimal wound disruption with less frequent changes of wounds. Debridement was added in two studies.^{45, 46} Compression, a key component of treating venous ulcers, was reported in six studies.^{22, 23, 34, 36, 40, 42} Skin grafting and immobilization was used in one study.³⁰

PRP formulation techniques and components, application techniques, frequency of application and “dosage”

Among the studies investigating PRP for treatment of lower extremity venous ulcers, formulation technique was variable. Most studies used a gel formulation for PRP application.^{22, 25, 30, 34, 40, 42, 45} One prepared PRP for application via dressing,²³ another applied PRP via injection to the wound bed.⁴⁶ One study compared outcomes between PRP injection to the wound bed, PRP application via dressing, and compression alone.³⁶ In terms of dosage, studies varied from up to 20 ml,^{30, 42, 45, 46} 9-30ml,³⁴ to maximum 7ml/kg.²³ One study did not state the volume of PRP used but suggested this was approximately 3-6 ml per treatment.³⁶ In terms of frequency, most studies provided weekly treatments,^{22, 25, 30, 34, 40, 42} three times a week,²³ once every 10 days,⁴⁵ biweekly³⁶ and only 1 time.⁴⁶ Total treatment duration varied, including 4 weeks,^{30, 40, 45} 6 weeks,⁴² up to 8 weeks,^{22, 36} 9 weeks,³⁴ up to 12 weeks,²³ 24 weeks.²⁵ A run-in period of two weeks was reported in one study.²⁵

Risk of bias

The overall risk of bias in the RCTs was moderate due to moderate risk of bias from randomization process (5 of 8) and measurement of outcomes (7 of 8) (Appendix Table G.1.). The overall risk of bias in the observational studies was high due to lack of comparability of study groups and independent blind assessment of outcome (Appendix Table G.2.).

PRP effectiveness and adverse events

Autologous Platelet-Rich Plasma

Table 4 lists the effectiveness of PRP when compared with management without PRP. Only one of two small RCTs showed a statistically significant reduction in pain scales when PRP was

applied; ²⁵ the second RCT showed nonsignificant difference.³⁴ Meta-analysis of these two RCTs was not feasible and the SOE was considered insufficient to draw conclusions about pain. There was no significant difference in the outcomes of complete wound closure (Appendix Figure Q.2.1.), wound infection (Appendix Figure Q.2.2.), wound recurrence, and wound area. There was no significant difference in total number of adverse events, number of withdrawals, and number of withdrawals due to adverse events (Appendix Table K.2.).

One RCT³⁰ compared PRP plus standard care to standard care after skin grafting procedure. There was no significant difference on complete wound closure between the two groups (RR= 1.17, 95% CI: 0.97 to 1.44).

Appendix Table J.2. summarizes the findings by individual studies.

Table 4. Comparisons of PRP versus management without PRP for lower extremity venous ulcers

Comparison	Outcome	Findings	Study Design, number of patients	Overall Evidence Strength (rationale)
PRP vs. Management without PRP	Complete wound closure	RR: 1.49.; 95% CI: 0.72 to 3.06; I ² =29.40%	4 RCTs ^{22, 23, 36, 40} and 1 comparative observational study; ⁴² 250patients	Insufficient (risk of bias and severe imprecision)
	Time to complete wound closure	WMD: 56 days, p>0.05 WMD: -90.00 days, 95% CI: -124.80 to -55.20, I ² =N/A	2 RCTs; ^{23, 36} 58 patients	Insufficient (risk of bias and severe imprecision)
	Wound recurrence	RR: 0.38; 95% CI: 0.09 to 1.57; I ² =N/A	1 RCT; ³⁶ 90 patients	Insufficient (risk of bias and severe imprecision)
	Wound infection	RR: 0.79.; 95% CI: 0.22 to 2.81; I ² =0.00%	3 RCTs; ^{34, 23, 36} 113 patients	Insufficient (risk of bias and severe imprecision)
	Pain scale (visual analog scale)	WMD: -1.75; 95% CI: -3.00 to -0.50; I ² =N/A WMD: -6.7; p=0.31	2 RCTs; ^{25, 34} 69 patients	Insufficient (risk of bias, inconsistency and imprecision)
	Quality of life (Chronic Lower Limb Venous Insufficiency Questionnaire, CIVIQ), higher means better outcome	WMD: 10.99 95%CI: -50.5 to 72.5; I ² =N/A	1 RCT; ³⁴ 8 patients	Insufficient (risk of bias and severe imprecision)
	Wound area (cm ²)	WMD: -1.17; 95% CI: -4.09 to 1.75; I ² =92.30%	2 RCTs ^{36, 40} and 2 comparative observational studies; ^{42, 45} 250 patients	Insufficient (risk of bias, inconsistency and imprecision)

CI = confidence interval; cm² = square centimeter; PRP = platelet-rich plasma; RCT = randomized controlled trial; RR= risk ratio; WMD= weight mean difference

Autologous Platelet Lysate

One RCT³⁵ compared autologous platelet lysate to placebo buffer solution in 86 patients with chronic venous leg ulcers. For up to 9-month treatment, there was no significant difference between the two groups on healing wounds (RR= 1.02, 95% CI: 0.81 to 1.27), time to complete wound closure (HR=0.88, p=0.37), and number of withdrawals (RR= 0.87, 95% CI: 0.29 to 2.65) (Table 5 and Appendix Table J.2.). There was no adverse event related to platelet lysate (Appendix Table K.3.)

Table 5. Comparison of autologous platelet lysate versus placebo buffer solution for venous ulcers

Comparison	Outcome	Findings	Study Design, number of patients	Overall Evidence Strength (rationale)
Autologous Platelet Lysate vs. placebo buffer solution	Complete wound closure	RR= 1.02, 95% CI: 0.81 to 1.27; I ² =N/A	1 RCT; ³⁵ 86 patients	Insufficient (risk of bias and severe imprecision)
	Time to complete wound closure	HR=0.88, p=0.37	1 RCT; ³⁵ 86 patients	Insufficient (risk of bias and severe imprecision)

CI = confidence interval; HR = hazard ratio; N/A = not applicable; RCT = randomized controlled trial; RR = risk ratio

Subgroup analysis

Appendix Table P.2. lists the subgroup analyses. We did not find significant difference on PRP formulation, activation, and administration route. A subgroup analysis of the control groups did not find significant difference between standard care and non-standard care.

Sensitivity analysis

We conducted sensitivity analysis by excluding high risk studies. No significant differences were found. (Appendix Table O.2.)

Pressure Ulcers

Key points

- Evidence was insufficient to estimate an effect of autologous platelet-rich plasma on wound area in patients with pressure ulcers.

Study characteristics

One RCT³⁸ and 1 comparative observational study evaluated PRP in pressure ulcers.⁴⁴ The comparative observational studies compared PRP to saline dressing in 50 pressure ulcers from 25 spinal cord injury patients,⁴⁴ while the RCT compared PRP to serum physiological dressing.³⁸ The average age of these patients was 57.64 years old; 41 percent were female with average BMI of 24.22. Mean duration of pressure ulcers was 72.80 days. Ulcers treated by PRP included Grade 2 (54.55%) and 4 (45.45%); while ulcers treated by management without PRP included Grade 2 (74.54%), 3 (7.27%) and 4 (18.18%). The length of followup after intervention was none to at least 6 months.^{38, 44} Appendix Table D.3., E.3., F.3., and H.3. list study characteristics.

In both studies^{38, 44}, wounds were first photographed and measured by a measuring tape. Wound areas were calculated by multiplying the length and the width. No inter-rater or intra-rater checker was reported^{38, 44} (Appendix Table I.3.).

Management without PRP

The observational study by Singh 2014 reported using debridement and saline dressing as the control intervention.⁴⁴ Ucar et al reported use of serum physiologic gas dressing as the control treatment.³⁸

PRP formulation techniques and components, application techniques, frequency of application and “dosage”

Both identified studies applied the treatment via gel to a gauze dressing, applying 30 ml on a biweekly basis for at least ten applications⁴⁴ or gel-impregnated gauze every 3 days for 2 months.³⁸

Risk of bias

The risk of bias in the RCT was moderate due to moderate risk of bias from randomization process, deviations from intended interventions, measurement of outcomes, and selection of the reported results (Appendix Table G.1.). The observational study was found to have high risk of bias due to lack of comparability of study groups and independent blind assessment of outcome (Appendix Table G.2.).⁴⁴

PRP effectiveness and adverse events

Autologous Platelet-Rich Plasma

No studies evaluated the outcome of complete wound closure. PRP significantly reduced more wound surface area than management without PRP^{38, 44} (Table 6 and Appendix Table J.3.), though the SOE was considered insufficient to draw conclusion.

Table 6. Comparison of PRP versus management without PRP for pressure ulcers.

Comparison	Outcome	Findings	Study Design, number of patients	Strength of evidence (rationale)
PRP vs. management without PRP	Wound area (cm ²)	WMD= -2.17, 95% CI: -3.16 to -1.19 ³⁸ WMD= -44.53, p<0.001 ⁴⁴	1 RCT, ³⁸ 60 patients and 1 comparative observational study; ⁴⁴ 50 wounds from 25 patients	Insufficient (risk of bias and imprecision)

cm² = square centimeter; PRP = Platelet-rich plasma; RCT = randomized controlled trial; WMD= weight mean difference

Patient Characteristics Commonly Considered for the Initiation and Continuation/Discontinuation of PRP in Patients with Chronic Wounds

Given the low number of overall studies in each category, we were unable to identify any differences in criteria for initiating or terminating PRP-based therapy for treatment of chronic wounds stratified by wound type. No study specifically described how the type of chronic ulcer (lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers) would

influence candidate selection or decision to terminate or complete treatment. Serra et al. was the only study to discuss utilization of ankle-brachial index (ABI) to categorize type of wound as arterial, venous or mixed, and we suspect this was due to the fact that this study combined surgical treatment with PRP-based therapy.³⁰ Most studies indicated that treatment was terminated if patients experienced an increase in wound size to the extent that they would require surgical treatment after commencement of therapy.

In the following paragraphs, we discuss criteria commonly considered for the initiation and continuation/discontinuation of PRP in patients with chronic wounds regardless wound type. Appendix Tables L.1. to L.3. list these criteria by each study.

Criteria commonly considered for the initiation and continuation of PRP therapy in patients with chronic wounds

Limb perfusion

11 studies cited adequate perfusion of any limb undergoing wound care treatment.^{20, 21, 23, 25-28, 30, 34, 41, 42} When specified, 5 studies used a value of 0.8 as a cut-off for study inclusion in venous ulcers.^{23, 25, 26, 34, 42} One study assessing venous leg ulcers used an ABI cut-off of 0.9.³⁶ In the case of one study utilizing platelet lysate as the experimental intervention ABIs were conducted to help make the determination of venous disease but not reported as a considered inclusion criterion.³⁵

Adequate glucose control

4 studies^{21, 25, 41, 42} specified adequate glucose control as a criterion for inclusion in patients with diabetes mellitus. When cited, the value for hemoglobin A1C (HbA1c) was typically ≤ 12 percent.

Platelet count

In order for prepared platelet products to have efficacy, it is commonly accepted that patients must not have known thrombocytopenia. 14 studies included a minimum platelet count for inclusion, generally ranging between 100,000-150,000 at a minimum.^{20, 21, 23-27, 31, 33, 36-38, 41, 42}

Failure of conservative standard care

Seven studies^{20, 24, 25, 32, 34, 36, 37} specified that patients must have failed conservative standard of care treatment prior to study inclusion; two studies^{21, 41} included a standard protocol for conservative management as a run-in to the treatment period and if patients improved with such a protocol to a significant degree they were not included in the study.

Wound grade

Not all studies specified wound grade in their consideration of inclusion for treatment consideration. There was some consensus that in general, wounds should not have exposed ligament, tendon or bone in order to be considered eligible for treatment with PRP or platelet products. Lower grade wounds (1-3) were most commonly listed as inclusion criteria when wound grade was a listed consideration,^{20, 21, 29, 31, 38} but two studies treated up through Grade 4,^{28, 44} and one up through Grade 5.²⁴

Wound size

Recommendations regarding ulcer size varied widely, from as small as 0.5 to as great as 50 cm². Larger wound sizes may have more difficulty with healing. There was no clear consensus on any limit to wound size.

Chronicity

Several studies noted that chronicity of wound was not considered clinically meaningful, as most ulcers are recurrent in this population. When chronicity of wound was listed as an inclusion criterion, most listed chronicity as 4 weeks or greater, although two studies^{20, 24} listed specifically 2 weeks of failed conservative care as the minimum length.

Criteria commonly considered for the discontinuation of PRP therapy in patients with chronic wounds

The only study that specifically defined criteria for discontinuation of PRP therapy for treatment of chronic wounds was Stacey et al.,³⁵ who considered failure of the wound to respond to therapy at 3 months or “dramatic increase in the size of the ulcer” as reasons to stop treatment with platelet lysate. Several studies mentioned that if wound closure was complete prior to the end of the planned treatment duration then therapy was considered complete.

Closure of wound undergoing treatment

Note that improvement is not immediate, and is expected to take more than 2 sessions to begin to show wound improvement (i.e. lack of immediate response was not a criterion for considering discontinuing therapy in any study). Several studies stopped therapy upon complete epithelialization of the index wound being treated.

Completion of therapy duration

The longest therapy duration was 9 months,³⁵ but most were 8-12 weeks in duration.^{20, 21, 23, 24, 26, 27, 32, 34, 36, 44} Several studies discontinued therapy in patients who developed severe or worsening infection despite treatment or those whose ulcer was progressing to the point of requiring surgery (this would be more likely to develop in patients with higher grade of ulcer at treatment initiation).

Key Question 2. What types of PRP preparations are currently being marketed in US medical practices (gel, liquid, etc.)?

Food and Drug Administration (FDA) has not licensed any PRP products for any specific indications. If a medical device is labeled or promoted for manufacturing PRP for the purpose of administering the device output to a patient, then the device would require FDA approval or clearance for that use prior to marketing in the United States. A physician may use a cleared or approved medical device for the treatment of a particular patient in a manner that differs from the cleared or approved indication (known as off-label use).

FDA has cleared medical devices that are indicated to prepare autologous PRP at the patient’s point of care. Known devices cleared for clinical use have been included in Appendix Table M.1. PRP preparations currently marketed in US medical practices are in 2 forms: autologous PRP in aqueous form for application with dressing or injection to the wound bed, or the gel form for application to the wound bed. The gel form can be produced from adding thrombin with or without calcium chloride to the PRP, or by centrifuging whole blood without

anticoagulant at low speed. Of each form, leukocyte count could be different depending on the provider's preference.

Key Question 3. What PRP preparations are currently being investigated in ongoing trials?

We identified 22 ongoing trials from trial registries⁴⁷⁻⁶⁸ (Appendix Tables N.1., N.2., N.3., N.4.). Six trials are being conducted investigating PRP therapy in lower extremity venous ulcers.^{47-49, 52, 57, 66} Only one trial reports specifies the study of plasma rich in growth factors (PRGF);⁴⁸ and another will use leukocyte-poor PRP;⁶⁶ otherwise there is no listed information among the studies in terms of specific PRP formulation. Three of the trials will use cutaneous applications including spray and emulsion,⁴⁷ concentrated solution,⁴⁸ and patch application.⁴⁹ One study reports utilization of a proprietary "Bio Matrix".⁵⁷ Another study will combine PRP with compression stockings.⁶⁶ The studies do not specify total treatment duration, but followup period is variable, including 9 weeks,^{49, 52} 12 weeks,^{47, 57} and one year.^{48, 66}

Twelve studies investigate PRP for the treatment of lower extremity diabetic ulcers.^{50, 51, 54, 55, 59, 61-65, 67, 68} None of the studies report details regarding PRP concentration or preparation. One study specifies PRP will be applied with daily saline dressing changes and debridement,⁵⁰ five report external application,^{50, 51, 61, 63, 65} one reports "intra-dermal" application,⁶⁷ and two studies include injection of PRP into the wound bed.^{50, 64} Study duration varies, and when specified is typically tailored according to length required to achieve wound closure. One study plans to administer PRP weekly for one month, then every two weeks for two months, then monthly until complete closure with no followup period specified.⁵⁰ Another study will apply treatment twice weekly for two weeks then weekly through the treatment period (which is not specified),⁶¹ a third study specifies only that PRP will be applied twice weekly,⁶³ and two studies will apply PRP weekly for three weeks⁶⁴ and four weeks.⁶⁷ One study plans to apply dressing with PRP every 3 days until 90% wound healing, with no specific end point cited.⁶⁵ Another study combines platelet-rich fibrin glue with vitamin E and vitamin C supplementation.⁶⁶ Followup period is variable, with most studies planning period of 4 weeks,^{64, 67} 8 weeks,⁶⁶ 16 weeks,^{51, 63} or 12 weeks.^{55, 59, 61, 62} Other studies did not specify planned followup time period.

Three studies plan to treat pressure ulcers at any location.^{53, 58, 60} The Cytomedix trial did not specify any details regarding PRP formulation, application technique, or study duration or followup period.⁵³ The PRP Concepts trial will study a proprietary fibrin matrix with no specified duration and followup period of 12 weeks.⁵⁸ The Nuo Therapeutic study plans to use a gel formulation applied externally twice weekly for two weeks then weekly throughout an undefined treatment period, with followup through 16 weeks.⁶⁰

The ACR Biologics study plans to investigate PRP treatment for a mixed variety of ulcers at any location, with weekly PRP application for 20 weeks with a followup period of 20 weeks.⁵⁶

The above clinical trials that are currently announced demonstrate the variety of preparation methods and applications of PRP therapy for wound care, but do provide more direction with respect to treatment duration and followup period.

Key Question 4. What best practices in study design could be used to produce high quality evidence on PRP?

For all three types of wounds, rigorous studies are still needed. RCTs need to be protected from selection bias with adequate allocation concealment and should have blinded outcome assessment. Prospective observational studies are also needed, but with clear stratification or

adjustment for important prognostic variables (wound duration, patient age and comorbidities, including diabetes control, arterial flow status with appropriate measurement, and venous insufficiency) as well as for co-interventions (e.g., debridement and offloading).

Future studies should focus on the characterization of the PRP products, with clear description of platelet concentration, key growth factor content, and leukocyte count. Detailed data on potential confounders such as body mass index, appropriately measured arterial perfusion, smoking status, occupation pertinent to weight bearing, and nutrition status should be collected and used when possible to stratify the results to allow better patient selection. Detailed description of the comparison group needs to be explicitly stated in future studies and conform to best practices in wound management. Outcomes, such as standardized wound classification complete wound closure, quality of life, psychological distress measures, and wound recurrence, need to be evaluated. Sample size calculations should be based on the baseline risk of these patient important outcomes, as opposed to power analysis based on changes in wound size. Long-term followup would be needed to examine the durability of the therapeutic effect. A 21-item checklist developed by the International Working Group of the Diabetic Foot (IWGDF) may be used to plan and report studies in diabetic foot ulcers.⁶⁹ In addition, studies using “big data” may also be useful to identify responsive population and provide guidance on life style modification that is critical for the success of the therapy.

Key Question 5. What are the evidence gaps found in this body of research?

Despite conducting a comprehensive literature search, we found a very small number of studies evaluating autologous PRP in three chronic wound etiologies. Data were particularly limited for lower extremity venous ulcers and pressure ulcers and the evidence to support PRP use in these two etiologies is insufficient. Although the three types of wounds studied share common pathophysiologic processes (local tissue hypoxia, bacterial colonization and an inflammatory environment)⁷⁰ extrapolation of efficacy across wound type would be challenging.

For venous and pressure ulcers, we simply need more studies. For lower extremity diabetic ulcers, evidence for effectiveness is available for wound healing outcomes; however, data are needed on the outcomes of amputation, infection, and hospitalization.

Discussion

Overview

This systematic review evaluated the effectiveness and safety of autologous platelet-rich plasma (PRP) therapy for chronic wounds, including lower extremity diabetic ulcers (14 randomized controlled trials [RCTs] and 1 observational study), lower extremity venous ulcers (7 RCTs and 3 observational study), and pressure ulcers (1 RCT and 1 observational study). In addition, 1 RCT evaluated autologous platelet lysate in patients with venous ulcers. Effectiveness and safety were assessed according to wound type.

Lower extremity diabetic ulcers have been studied the most. PRP therapy significantly increases complete wound closure (moderate strength of evidence [SOE]), shortens the time to complete wound closure, and reduces wound area and depth (low SOE), compared with management without PRP. No significant changes were found in terms of wound infection, amputation, wound recurrence, or hospitalization. In patients with lower extremity venous ulcers,

for critical outcomes, such as complete wound closure, or time to complete wound closure, the evidence was insufficient and the estimates were statistically nonsignificant. Similarly, evidence was insufficient to estimate an effect on any outcome in pressure ulcers.

In terms of safety, there was no clear signal of harm for all three wound types. There were no statistically significant differences in death, total adverse events (AE) or serious adverse events between PRP and management without PRP. These data were primarily from the studies of PRP in diabetic ulcers; with much less AE data in venous and pressure ulcers. From clinical perspective, patients and clinicians would be concerned about dermatologic, hematologic, neurologic, and rheumatologic AE. These were not statistically significantly different between PRP and management without PRP; although these analyses are clearly underpowered.

Findings in Relation to What Is Known

Lower Extremity Diabetic Ulcers

Few current guidelines discussed PRP therapy in lower extremity diabetic ulcers.⁷¹⁻⁷³ The Wounds International 2013 guideline recommended adjunctive PRP therapy when wounds did not respond to standard care;⁷¹ while NICE (National Institute for Health Care Excellence) 2015 (updated in 2019) guideline and the Wound Healing Society (WHS) 2016 guideline recommended not to use PRP in any condition.^{72, 73}

Our systematic review found moderate strength of evidence suggesting effectiveness for complete wound closure in lower extremity diabetic ulcers. Guidelines emphasize that PRP therapy for lower extremity diabetic ulcer is not meant to replace other multidisciplinary and comprehensive wound care interventions. Rather it should be viewed as a possible adjunct therapy. The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine recommends glycemic control, appropriate debridement, custom therapeutic foot ware for high risk patients, off-loading and followup by x-ray or magnetic resonance imaging if infection occurs. PRP therapy is intended to stimulate and speed up healing, but it is essential that all those conventional measures are followed to assure the success of the healing process.

An optimal outcome of wound care is to achieve complete wound closure with re-epithelialization that stops discharge and reduces the risk of infection, tissue necrosis, and osteomyelitis, which are complications known to increase the risk of subsequent lower extremity amputation. Unfortunately, complete wound healing is hard to accomplish in the majority of patients with standard care measures,⁷⁴ which has a strong impact on patient's quality of life. A systematic review examined the control group of 10 clinical trials with a total of 622 patients with diabetic foot ulcers. The healing rate was found to be only 24 percent at 12 week and 31 percent at 20 week.⁷⁵ A prospective study estimated the complete healing rate to be 46 percent at one year.⁷⁶ These data emphasize the challenge of healing diabetic ulcers that patients experience in the real world.

In addition to a good outcome of healed wound, another outcome that is highly important to patients is the healing speed. Chronic wounds heal slowly, which hampers the compliance to the recommendations of off-loading and other appropriate wound care.^{77, 78} In addition, the longer the healing takes, the higher risk the patient is exposed to infection. A study tracking the timeline of 105 patients showed that in those patients who received standard comprehensive specialty wound care and healed, the median time from start of treatment to healing was 75.5 days.⁷⁹ Comparison of healing time between PRP and control group was reported in 4 studies, of which

3 reported statistically significant reduction and 1 showed no difference. The strength of evidence is low due to increased risk of bias and imprecision (small sample size) of the available studies; suggesting that there may be some uncertainty about these estimates and perhaps patients with different characteristics may respond differently.

Chronic wound pain can be debilitating and a source of mental stress as it prevents patients from ambulation and imposes suffering during dressing change and debridement.^{80, 81} The pain has been found highly prevalent with 75 percent of patients reporting worsening pain with walking and 80 percent with dressing change.^{82, 83} Because of their complex and chronic nature, pain reduction as early as possible has been a key clinical goal. Unfortunately, wound pain is recalcitrant and has been associated with chronic pain features such as pain centralization and chronic opioid use.⁸⁴⁻⁸⁸ PRP therapy has been evaluated in this systematic review with mixed results. In an RCT with 76 patients, pain was found to be significantly reduced in the PRP group compared with management without PRP. In another RCT with 269 patients, no significant difference was found. As the pain is associated with stimulation from local inflammatory microenvironment,⁸⁹ it is not surprising that as PRP is not a strong pain inhibitor as it does not possess a strong immunomodulatory effect.

Wound infection is defined as microorganisms' invasion and multiplication in the wound that induces a host inflammatory response, often leading to tissue destruction.^{90, 91} In lower extremity diabetic ulcers, infection often requires hospitalization and is a main predictor of amputation. PRP has been reported to exert anti-microbial effect in preclinical studies,⁹² but the magnitude of this effect has not been widely reported as being clinically relevant. In this systematic review, the effect of PRP on wound infections did not achieve statistical significance (insufficient SOE).

Lower extremity diabetic ulcers contribute to 48 percent of all lower extremity amputations,⁹³ with more than 80,000 amputations annually in the United States for failure of conservative treatment leading to unsalvageable diabetic foot.⁹⁴⁻⁹⁶ In our systematic review, the amputation rate in patients treated without PRP was only 8.29 percent (95% CI: 3.52% to 13.05%). This low rate may be unique to the research setting, but it suggests the need for a larger sample size to demonstrate an effect of PRP on amputation.

Lower Extremity Venous Ulcers

No clinical guideline discussed PRP therapy in venous ulcer. In contrast to lower extremity diabetic ulcers, pain is reported as often the first symptom in patients with venous ulcer and the prevalence of severe pain is reported to be as high as 64 percent,⁹⁷ and it affects activities of daily living, sleep pattern, mobility and psychological functions.⁹⁸ In this systematic review, one RCT²⁵ reported that PRP therapy was associated with significant pain relief, while another study³⁴ did not show significant change. Further studies are needed to evaluate the effect on pain, considering the importance of pain in affecting quality of life and mental status in these individuals. PRP may reduce pain by modulating inflammatory mediators and cytokines.^{99, 100} Two RCTs and 2 observational studies found no significant reduction in wound size. This evidence base was imprecise, inconsistent with increased risk of bias. Thus, conclusions are not possible at the current time to determine whether PRP affects wound healing.

Pressure Ulcers

Two current guidelines supported use of PRP in advanced pressure ulcers or ulcers that have not responded to initial therapy.^{101, 102} We did not find sufficient direct evidence on use of PRP for pressure ulcers. We only found 2 small studies (1 RCT and 1 observational study) evaluated

PRP for pressure ulcers. No possible conclusions can be made estimate an effect on any outcome.

Limitations

We were unable to identify ideal patient characteristics to initiate, continue, or discontinue PRP. Our findings were limited by lack of standard reporting of the following: 1) PRP formulation techniques (centrifuge type, centrifuge speed, centrifuge time, radius of rotor); 2) PRP concentration, formulation and volume used; 3) lower extremity diabetic ulcer offloading procedures and periprocedural restrictions; 4) patient recruitment methods including underrepresentation of older adults, followup procedures and run-in periods. Our findings are based on studies that differ from a real world Medicare population, particularly not including older patients. In addition, qualitative and quantitative syntheses were restricted by heterogeneity of the included studies, in terms of patient population, inclusion/exclusion criteria, wound severity, use of PRP (formulation, application techniques, frequency, dosage, duration of treatment), outcome assessment, length of followup, and study design. The evaluation of adverse events was also limited by the fact that 39 percent of the included studies (9/23) did not evaluate adverse events and majority of the rest did not use a consistent approach for reporting and evaluation. We could not statistically evaluate publication bias in almost all of the comparisons because the number of studies included in these comparisons was small ($n < 10$). We judged the included studies to have moderate to high risk of bias because of potential deviations from intended interventions, missing outcome data, bias from randomization process, lack of comparability between study groups and lack of independent blind assessment of outcomes. Finally, failure to detect statistical significance for many of the outcomes could have resulted from small sample size and lack of power

Applicability

The available studies did clearly present or stratify the results based on several important factors needed to determine patients who are candidate for PRP therapy, such as age, race, ethnicity, socioeconomic status, vascular status or patient comorbidities. Furthermore, several other issues were noted to affect the applicability of the findings. First, there is a concern of heterogeneity of PRP preparation technology that varies between different providers. Secondly, each patient's platelet count in the blood is different. As a result, the product may vary in the amount of platelets per volume unit. The number of white blood cells (WBCs) is different in each preparation, and the growth factor content may vary between patients. Thirdly, there are not enough data to differentiate if one PRP formula or route of application would be superior to another. The most common formulation is gel applied directly to the wound bed. All these differences may limit the ability of a health system or a healthcare provider to implement the intervention as evaluated in published studies. In addition, the effect of dressing is different in each one of the studies and not clearly described or standardized. Fourthly, this systematic review included studies that were conducted in various locations across the globe that may not be representative of patients in the United States. Lastly, patients in randomized controlled trials may significantly differ from those encountered in practice, including underrepresentation of older adults. Considering the common description of the interventions and patients across the majority of the studies, the results are likely most applicable to PRP in gel formulation, given every 1-2 weeks for 1-3 months, to patients aged 40-70 who had cardiovascular comorbidities such as smoking, hypertension, peripheral artery disease or chronic kidney disease.

Conclusion

In individuals with lower extremity diabetic ulcers, autologous platelet-rich plasma increases complete wound closure (moderate SOE), shortens healing time (low SOE) and reduces wound size (low SOE). The evidence is insufficient to estimate an effect of autologous platelet-rich plasma on wound healing in individuals with lower extremity venous ulcers or pressure ulcers.

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Abbreviations and Acronyms

ABI	ankle-brachial index
AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CI	confidence interval
CM	centimeter
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FGF	fibroblast growth factor
HbA1c	hemoglobin A1c
HGF	hepatocyte growth factor
HR	hazard ratio
IGF	insulin growth factor
ITT	intention-to-treat
IWGDF	International Working Group on the Diabetic Foot
KQ	key questions
MHRA	Medicines and Healthcare Products Regulatory Agency
ML	millimeter
NA	not applicable
NICE	National Institute for Health Care Excellence
PAD	peripheral arterial disease
PDGF	platelet-derived growth factor
PICOTS	population, Interventions, Comparisons, Outcomes, Timing, and Setting
PPP	platelet-poor plasma
PRGF	plasma rich in growth factors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	platelet-rich plasma
RCTs	randomized controlled trials
RR	risk ratio
SES	socioeconomic status
SOE	strength of evidence
US	United States of America
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHS	Wound Healing Society
WMD	weight mean difference