Technology Assessment Program

Platelet-Rich Plasma for Wound Care in the Medicare Population

Technology Assessment
Project ID:MYOE59
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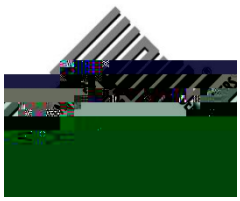

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Platelet-Rich Plasma for Wound Care in the Medicare Population

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Key Messages

Purpose of review

To evaluate the effectiveness of a

This report is based on research conducted by the Myth Evidence

Disclaimer:
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).

Preface

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: from the Agency for Healthcare Research and Quality our task order officer: David W. Niebuhr, M.D., M.P.H., M.Sc. and Elise Berliner,.Ph

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 $5,000and 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

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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 nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential 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 and 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, 10 (g)10 u(e)4 (c5 (e)-2 (i)-2)]TJ -0.2 (h)-10nenrolled x e w o l t (a)-4 bce14(5 (i)-6 Tc r-0.002 Tw c[(p)2 (a)6e0(P)-8 (ai)-6(p6-1o(a)6mo(a)6it)-1b)-2 (b)-8 ((t

Contents

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-plasma on wound healing in individuals with lower extremity venous ulcers.
- Evidence is insufficient to make conclusions about the effect of autologous platelet-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-plasma formulation te-1 (P-6 (at)-5.9>(t)-2 (rd [(p)9 (el)-5.9 (et)]TJ 0 Tc 0 (i50.004 Tc 0Ed [(T)-e0.004 T

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 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 environment),[60] 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 AEs. 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.

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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.[4] 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-

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

(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:

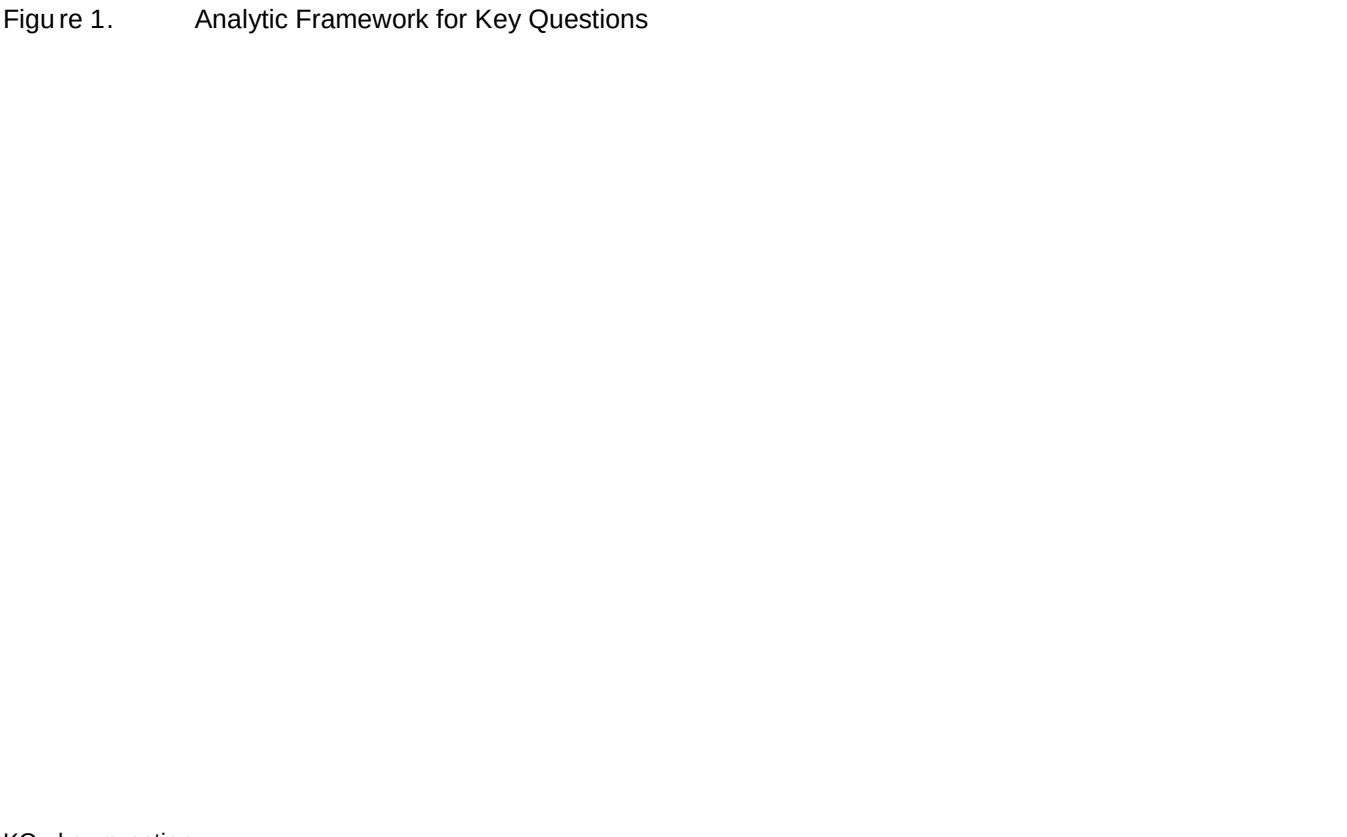
KQ4. What best practices in study design could be used to produce high quality evidence on PRP?

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 rew (t)- (n pa)4 (e)4o2

Figure 1. Analytic Framework for Key Questions



KQ= key question

1. Literature Search Strategy

a. Search Strategy

We conducted a comprehensive search of 8 bibliographic 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 p ( )Tj 0.01 Tw [(3ir76IJ -)Tj m (

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

extraction, and resolve conflicts. When the included studies did not report all necessary

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=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

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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

8 r (The literature search identified 4,14 4) 2 -47 J

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 study[43] with 1,096 patients evaluated autologous

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 in 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 n3-2 (on7.1 (y)-P)-10 R-2 (uP)-10

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 RCT[30] 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%	7RCTs;[21, 24, 26, 28, 31, 33, 41] 717 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 cm^2; 95% CI: -3.03 to -0.67 vs. non-activated PRP: -0.10 cm^2; 95% CI: -0.15 to -0.06). Subgroup analysis based on length of followup (<6 weeks vs. >=6 weeks) showed (i) inpatient vs. (act)-6 (i)-6 (v 7.81w 7

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

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 RCT[30] 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 1.41).

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)

Autologous Platelet Lysate

One RCT[35] 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

influence candidate selection or decision to terminate or complete treatment. Serena 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 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 cm^2. 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. While 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

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 registries[47-68] (Appendix Tables N.1., N.2., N.3., N.4.). Six trials are being conducted investigating PRP therapy in low be8

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 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 healing, 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. The 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,?

for critical outcomes, such as complete wound closure, or time to complete wound closure

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

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, r

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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