Autologous blood products

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BMJ Open

Autologous blood products: Leucocyte and Platelets Rich Fibrin (L-PRF) and Platelets Rich Plasma (PRP) gel to promote cutaneous ulcer healing – a systematic review

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ABSTRACT

Objective To summarise evidence on the effectiveness of Platelet-Rich Plasma (PRP) gel and Leucocyte and Platelet Rich Fibrin (L-PRF) gel as agents promoting ulcer healing compared with the standard wound dressing techniques alone.

Design Systematic review.

Eligibility criteria Individual patient randomised controlled trials on skin ulcers of all types excluding traumatic lesions.
Intervention group: treatment with topical application of L-PRF gel or PRP gel to the wound surface.
Control group: treatment with standard skin ulcer care using normal saline, normgel or hydrogel dressings.

Information sources Medline (Ovid), Excerpta Medica Database (EMBASE), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science and manual search of studies from previous systematic reviews and meta-analyses. The papers published from 1946 to 2022 with no restriction on geography and language were included. The last date of the search was performed on 29 August 2022.

Data extraction and synthesis Independent reviewers identified eligible studies, extracted data, assessed risk of bias using V.2 of the Cochrane risk-of-bias tool for randomised trials tool and assessed certainty of evidence by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Main outcome measures Time to complete healing, proportion healed at a given time and rate of healing.

Results Seven studies met the inclusion criteria, five using PRP gel and two using L-PRF gel. One study showed a better proportion of complete healing, three reported reduced meantime to complete healing and five showed improved rate of healing per unit of time in the intervention group. The risk of bias was high across all studies with one exception and the GRADE showed very low certainty of evidence.

Conclusion The findings show potential for better outcomes in the intervention; however, the evidence remains inconclusive highlighting a large research gap in ulcer treatment and warrant better-designed clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review is designed in accordance with standard systematic review protocol guidelines.
⇒ We restricted our control procedures to exclude other treatments of unknown effectiveness.
⇒ We only included randomised control trials to represent studies with stronger evidence on the effectiveness of the intervention.
⇒ We did not restrict language or regions for better global representation.
⇒ We could not perform a meta-analysis, in part because some outcome proportions were zero and measures of uncertainty were not provided in some primary studies.

PROSPERO registration number CRD42022352418.

INTRODUCTION

Non-healing cutaneous ulcers remain a challenge for patients and clinicians.[1] Skin ulcers often heal slowly, particularly when accompanied by a combination of vascular insufficiency, neuropathy and deformity induced by peripheral sensory-motor neuropathy such as diabetes and leprosy.

The currently available standard treatment methods for chronic ulcers include ulcer bed debridement, moist wound dressing, exudate control, offloading, metabolic control such as blood glucose control and infection control with antibiotics.[2] Complete wound closure with these standard treatment approaches takes time (months or even years) and in some patients wound closure fails. Slow and incomplete healing has stimulated a search for alternatives that may promote ulcer healing in a short time. The application of platelet-rich concentrates is one such approach.[3]

Platelet concentrates are used in most medical fields like in sports medicine and orthopaedic surgery.[4] Based on the content of leucocyte and fibrin, platelets concentrates are categorised under four categories: (1) pure platelet-rich plasma (PRP), (2) leucocyte and platelet-rich plasma (LPRP), (3) pure platelet-rich fibrin (PRF) and (4) leucocyte and platelet-rich fibrin (L-PRF).[5] PRP gel is a coagulated mixture of PRP with thrombin or calcium and is an inexpensive and immunologically safe source of different growth factors and is believed to accelerate the wound healing process.[6] PRF/L-PRF gel is a second-generation platelet concentrate that contains leucocytes in addition to PRP gel potentially providing antibacterial activity and additional growth factors.[7] PRP gel and L-PRF gel release a variety of concentrated growth factors including platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor, epidermal growth factor, fibrinogen and insulin-like growth factor.[8] The growth factors released from the α-granules of activated platelets, along with fibrin, fibronectin and vitronectin are believed to play an important role in the modulation of tissue repair and regeneration and have been likened to the healing effects of a scab in a traumatic wound.

Previous systematic reviews and meta-analyses evaluated the evidence comparing L-PRF gel or PRP gel with a wide range of control groups including standard care, antiseptic ointment, hyaluronic acid, platelet-poor plasma (PPP).[1 9–12] In this paper, we focus on studies comparing blood products with standard care rather than alternative treatments of unknown effectiveness. However, meta-analysis could not be performed as there were too few studies.

Therefore, the purpose of this systematic review was to summarise the current evidence on the effectiveness of PRP gel and L-PRF gel as agents promoting ulcer healing compared with standard wound dressing alone.

Review questions and objectives

We systematically reviewed the literature to identify individual-level randomised controlled trials (RCTs) reporting the estimated treatment effects of PRP gel and L-PRF gel compared with standard treatment on the healing of non-traumatic skin ulcers. There are several related ways of specifying the treatment effect. We included trials that estimated the difference in any of the following outcomes between PRP gel or L-PRF gel and standard treatment:

1. Proportion of cutaneous ulcers that are completely healed (re-epithelialised) by a prespecified time point.
2. Time to complete healing (re-epithelisation).
3. Rate of healing of cutaneous ulcers (eg, cm^2 per unit time).

METHODS

The systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Online supplemental table 1).[13] The protocol is registered with the International Prospective Register of Systematic Reviews PROSPERO (CRD 42022352418).[14]

Eligibility criteria

We included articles that met the following inclusion criteria:

1. Study types: individual patient randomised controlled studies published in scholarly/academic journals with full text available.
2. Population: adult patients with any non-traumatic skin ulcers including leprosy, diabetes mellitus, venous insufficiency and pressure sores.
3. Intervention: treatment of skin ulcers using topical applications of L-PRF gel or PRP gel.
4. Control groups: treatment with the standard treatment such as the use of normal saline or normgel or hydrogel dressing.
5. Outcome: the proportion of ulcers completely healed, time to complete healing, the rate of healing per unit time.

The exclusion criteria were:

1. Patients with traumatic wounds including burn injuries.
2. Patients who underwent injectable PRP in the intervention group rather than surface application.

We included papers published from 1946 to 2022 with no restriction on geography and language. The last search was performed on 29 August 2022.

Information sources

We searched five databases: Medline (Ovid), EMBASE (Ovid), Scopus, CINAHL and Web of Science to identify individual-level RCTs reporting the estimated treatment effects of L-PRF gel and PRP gel on the healing rates of non-traumatic skin ulcers.

We also searched for any systematic reviews dealing with the effectiveness of PRP/L-PRF gel. We then searched the references included in these systematic reviews to identify any studies that were not included in our above search.

Search strategies

We used the following keywords and their related terms to search from the above-mentioned databases: autologous blood product, L-PRF gel, PRP gel, PRP and cutaneous ulcers. The details of the keywords and related terms along with the search strategy for each database are presented in online supplemental table 2.

Selection process

We used the reference manager software (Zotero)[15] to manage the study retrieval, storage, selection and deduplication process. We first divided seven reviewers into two groups (IBN/DS/RD/LG and KN/AA/RK). A member from each group independently screened titles and abstracts. The two groups then came together to compare their selected studies and decided on a long list of studies for full-text screening. The selected full texts were then scrutinised by each member of the above groups in order to make a final selection of eligible studies.

Data collection process

Independent reviewers (RD/LG and KN/AA/RK) in the two groups reviewed and extracted data from selected articles into summary tables. We summarised the data in a standardised form to include the first author, year of publication, mean age, the sample size in each trial arm, intervention type (PRP gel or L-PRF gel), control type (normal saline or normgel or hydrogel dressing) and duration of follow-up.

Data items

We sought data for three treatment effects for both intervention and control groups:

Outcome 1: Proportion of complete healing at a specified time period from randomisation.

Outcome 2: Time to complete healing in days or weeks.

Outcome 3: Rate of healing reported in terms of area of wound healing in cm^2 per unit time (days or weeks).

Other data extracted included baseline characteristics such as the age of the participants, ulcer types, types of intervention and baseline ulcer size and duration of ulcer.

Risk-of-bias assessment

We assessed the risk of bias in the included studies using V.2 of the Cochrane risk-of-bias tool for randomised trials (RoB2) tool.[16] The RoB2 tool assesses five domains of bias as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessments (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential bias.

We divided the reviewers into two groups (IBN/DS/RD/LG and KN/AA/RK) and one member of each group assessed each study for risk of bias independently. Each group followed the full guidance document as outlined by RoB2 tool to judge the individual studies for risk of biases as 'high', 'some concerns' and 'low'. According to the Cochrane Handbook,[17] an RCT is judged to be at overall low risk of bias if all domains have low concerns, an RCT is judged to be at overall some concerns if at least one domain has some concerns and an RCT is judged to be at overall high risk of bias if at least one domain has high concerns or some concerns for multiple domains. The two groups then discussed the independent judgments together and made the final decisions by resolving any disagreements.

Data synthesis and statistical analysis

We performed the narrative synthesis of the included studies and summarised the characteristics of the studies. We reported the outcome (time to healing, proportion healed, rate of healing) including the point estimate, and any uncertainty measures including SE, p value and 95% CI. We planned to perform a meta-analysis and estimate a pooled mean difference, risk ratio and HR relating to each of our outcomes. However, there were too few studies to conduct a random effects meta-analysis with any outcome and a fixed effects analysis was not considered appropriate given the heterogeneity between the studies in terms of treatment, population and other aspects of the study design. Therefore, we changed the study to a systematic review from systematic review and meta-analysis.

Certainty assessment

We assessed the certainty of the evidence for all three outcomes using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[18] We used the GRADEpro software to manage and summarise the included studies and evidence.[19] The GRADE approach comprises five factors: risk of bias, precision, inconsistency, indirectness and publication bias. According to the GRADE, the initial certainty of the evidence for RCT is considered to be high with a total score of four. The reviewers then downgrade the scores depending on the seriousness that may affect the certainty of the evidence for each factor mentioned above. The reviewers can downgrade the score by one (−1) for serious concerns and by two (−2) for very serious concerns or do not downgrade if there are no concerns. The final score is the sum of the scores of all the factors which could be high (4), moderate (3), low (2) or very low (1) for the certainty of evidence. As before, reviewers were divided into two groups, performed the assessments independently and made the final decisions together by resolving disagreements.

Patient and public involvement

No patients involved.

RESULTS

Study selection and characteristics

Figure 1 summarises the identification of the studies and each step of the screening process with the PRISMA flow diagram 2020.[13] We identified 1083 studies from 5 databases (Medline, EMBASE, Scopus, CINAHL and Web of Science) and manual search from previous systematic review and meta-analysis. From the databases, we removed 641 duplicates. After screening 442 studies based on title and abstracts, we sought retrieval of 23 studies for full-text screening. This was only possible for 20 studies since 3 studies could not be located online or through our university libraries. Seven studies met the criteria for final review after the full-text screening. Among the 13 excluded studies, 1 study was not RCT, 1 was a conference article, 2 had a different ulcer type, (ie, traumatic ulcer), 8 compared treatment or control groups that differed in other aspects apart from the index therapy (ie, PRP gel or L-PRF gel) or standard treatment as defined above and 1 study had a different outcome other than ulcer healing. The process of screening and inclusion of the studies is outlined in the PRISMA flowchart (figure 1). We have provided the details of excluded studies based on full-text screening in online supplemental table 3.

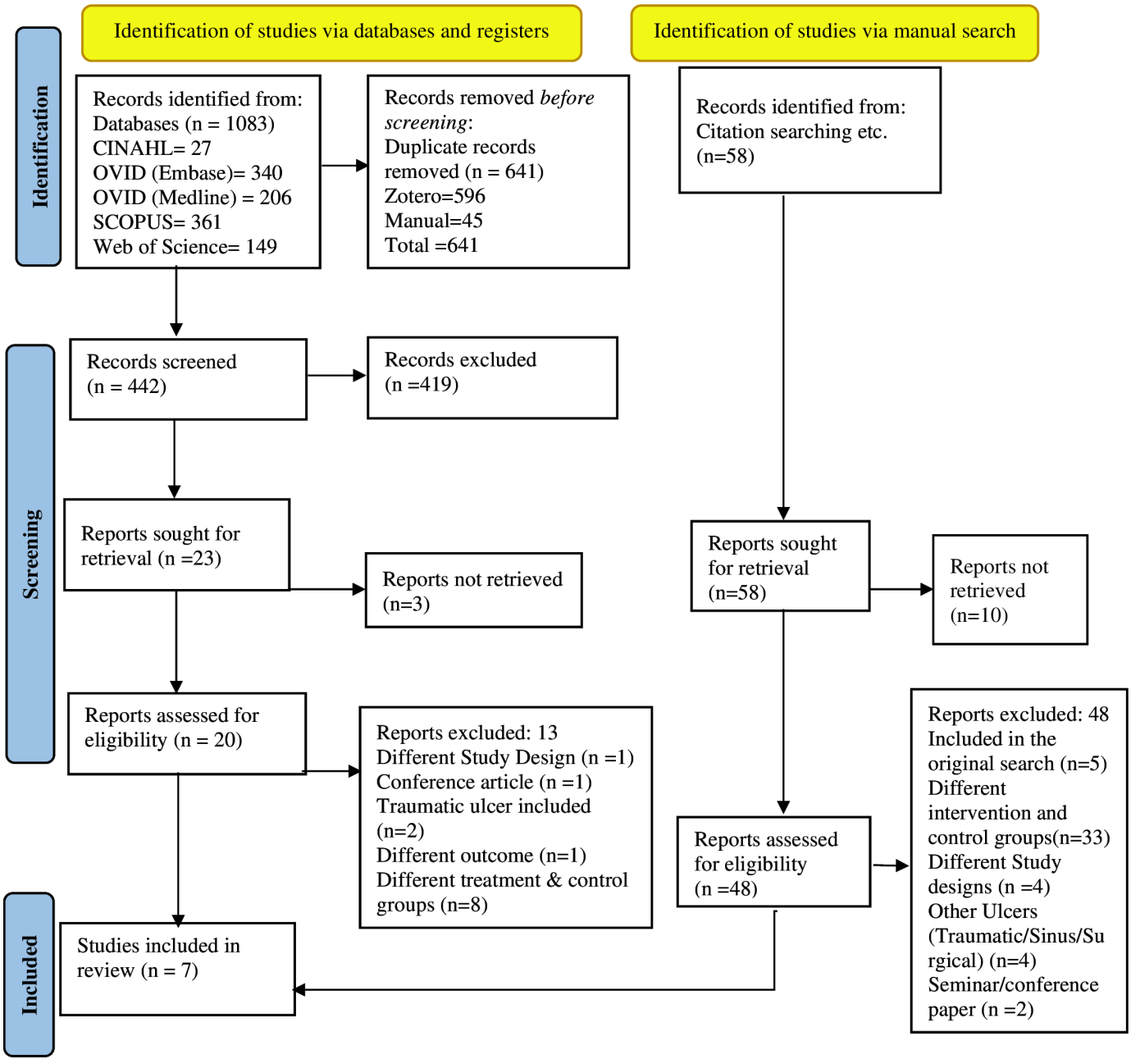

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

We manually searched for other systematic reviews dealing with L-PRF/PRP and found eight more systematic reviews. While these reviews had explored the same topic as those in our review, the objectives and inclusion criteria differed. On searching the cited references of these 8 systematic reviews, we found 58 studies but 10 of these studies could not be retrieved, as shown in PRISMA flowchart (figure 1). In total, 43 of the remaining 48 studies did not meet our eligibility criteria for reasons laid out in online supplemental table 4 (the main reasons for exclusion were control groups that received non-standard treatments or additional interventions in the L-PRF/PRP gel group). This left five eligible studies among the reviewers and all of these had already been included in our systematic review as summarised in online supplemental table 5. Then online supplemental table 6 summarises the two new studies we had identified through databases search that were not included in previous systematic reviews.

Table 1 summarises the baseline characteristics of the seven included studies. Only two studies, Goda[20] and Somani and Rai[21], had L-PRF gel as an intervention, the remaining five had PRP gel. Among the seven studies, two were conducted in India,[21 22] two in Egypt,[20 23] and the remaining studies were conducted in the USA,[24] China[25] and Turkey,[26] respectively. Four studies were conducted in patients with diabetic ulcers,[22–25] two in patients with venous leg ulcers[20 21] and one in patients with pressure ulcers.[26]

Only five studies reported the proportion of ulcers completely healed, four studies reported time to

Table 1 Baseline characteristics of the individual studies

Study/country	Type of ulcer/ outcome (1,2,3)*	Intervention group			Control group		
		Duration of ulcer mean, (SD)	Ulcer size mean, (SD)	Total (n)	Duration of ulcer mean, (SD)	Ulcer size mean, (SD)	Total (n)
PRP gel group							
Rajendran *et al*[22] India	Diabetic (1,3)	NR	42.9 (19.4)	60	NR	40.7 (18.6)	60
Driver *et al*[24] USA	Diabetic (1,2,3)	NR	Area 3.4 (4.5) cm^2 Volume 0.9 (1.3) cm^3	19	NR	Area 3.6 (4.0) cm^2 Volume 1.0 (1.4) cm^3	21
Li *et al*[25] China	Diabetic (2,3)	Median (IQR) days 30 (15–90)	Median (IQR) 4.1 (1.4–11.4)	59	Median (IQR) days 23 (14–60)	Median (IQR) 2.9 (1.0–10.5)	58
Uçar and Çelik[26] Turkey	Pressure (1)	NR	8.4 (2.3)	30	NR	9.5 (2.2)	30
Elsaid *et al*[23] Egypt	Diabetic (1,2)	5.3 (3.4) months	4.6 (2.5) longitudinal diameter and 5.4 (3.4) horizontal diameter	12	5.6 (2.7) months	4.0 (1.5) longitudinal diameter and 3.8 (1.4) horizontal diameter	12
L-PRF gel group							
Goda[20] Egypt	Venous (2,3)	NR	<10 cm^2=10 >10 cm^2=8	18	NR	<10 cm^2=11 >10 cm^2=7	18
Somani and Rai[21] India	Venous (1,3)	NR	8.1 cm^2	9	NR	4.8 cm^2	6

*1 represents the proportion of ulcers completely healed, 2 represents the time to complete healing and 3 represents the rate of healing per unit time (cm^2 per week).
L-PRF, leucocyte-rich and platelet-rich fibrin; PRP, platelet-rich plasma.

complete healing and five studies reported the rate of healing per unit of time. Five studies reported mean age in years at baseline in terms of mean and SD[21–24 26] The mean age (SD) ranged from 39.3 (8.2) to 68.3 (6.4) years. The sample size ranged between 9 and 60 subjects in both intervention and control groups. The mean ulcer size ranged from 8.1 to 42.9 cm^2 at baseline across the seven studies (table 1).

Within the seven included studies, there is a variability in the method of ulcer measurements. Rajendran *et al* measured the ulcer area using the measurement (length and breadth) taken with the help of vernier callipers and marked on graph paper.[22] Li *et al*[25] calculated the area using the picture processing software ImageJ V.1.46h (National Institute of Health, Bethesda, Maryland, USA).[27] Somani and Rai measured the longest length and longest breadth using a thread and scale using the clock face method.[21] Goda measured the length and breadth of the ulcer every week using metric tape and calculated the area.[20] Uçar and Çelik calculated the area by multiplying the length and breadth of the ulcer.[26] The method used for length and breadth measurement was not stated clearly. Driver *et al* used metric tape to measure the length and breadth of the ulcer and calculated the area of the ulcer.[24] Elsaid *et al* used measuring tape to measure the length and width of the ulcer and calculated the ulcer area.[23]

Variability in PRP gels

It was found that there was no uniformity in the techniques followed by the different studies to prepare the PRP gel. Rajendran *et al* followed the double spin method. In the first spin, 20 mL of venous blood was collected in a tube containing acid dextrose solution and then centrifuged at 5000 rpm for 15 min.[22] This first spin was to separate the supernatant and buffy coat from the red blood cells. The buffy coat and supernatant were transferred to another tube and was again centrifuged at 2000 rpm for 5–10 min. About 1.5 mL bottom layer was taken out and mixed with 10% calcium chloride. The activated PRP was then applied to the ulcer bed. Driver *et al* collected 20 mL of blood and centrifuged in a portable centrifuge for 1.5 min to separate PRF from whole blood.[24] The extracted PRP was then mixed with reagents to form the PRP gel. Li *et al* collected 20–100 mL blood in a sterile centrifuge tube containing 2–10 mL

anticoagulant (PH 8) and centrifuged at 313× *g* for 4 min. The red blood cell concentrate was removed and the remaining plasma was further centrifuged at 1252× *g* for 6 min to separate PRP from PPP which was then mixed to thrombin and calcium gluconate in a proper proportion of 10:1 to form the PRP gel. Uçar and Çelik collected 10 cm^3 blood from the patients in sodium citrate blood tubes and centrifuged at 2000 rpm for 5 min.[26] The prepared PRP gel was separated from the tube and placed on sterile gauze. Elsaid *et al* collected 20 mL of venous blood in a tube containing citrate dextrose and two rounds of centrifugation were performed. The first spin was done at 3600 rpm resulting in three layers. The top two layers (PPP and PRP) were collected in another tube and centrifuged at 2400 rpm. The bottom portion was taken out and mixed with 20% calcium chloride solution to form the PRP gel.[23]

Risk of bias

Online supplemental figure 1 (traffic light plot) demonstrates the risk of bias for the individual domains of each study. Six studies[20–24 26] had an overall high risk of bias with only one study showing a low risk of bias. For domain 1 on bias arising from the randomisation process, two studies[21 22] showed a high risk of bias and two showed some concerns. For domain 2 on bias due to deviation from the intended intervention, two studies[21 24] showed a high risk of bias and four studies showed some concerns. For domain 3 on bias due to outcome data and domain 4 on bias in the measurement of outcome, only one study[23 24] each showed high risk and the remaining studies showed low risk. For domain 5, four studies[20–22 26] showed some concerns and the remaining studies showed low risk. The study by Li *et al*[25] showed the lowest risk of bias by a considerable margin.

Summary of treatment effects

Proportion healed completely

Table 2 summarises the characteristics of the studies reporting this outcome. Four studies[22–24 26] based on PRP gel and one study based on L-PRF gel reported the proportion of ulcers healed completely. In Driver's study of PRP gel,[24] a risk ratio of 1.6 (95% CI: 0.9 to 2.9) was found in favour of the intervention even though it was not statistically significant. The proportion of the ulcers that healed completely was zero in the control groups of the remaining three PRP gel studies[22 23 26] with the result that risk ratios, 95% CI and p values could not be calculated. In the particular case of the study by Uçar and Çelik,[26] no ulcers healed completely in either intervention or control groups. The single L-PRF gel-based study that observed this outcome also registered no cases of complete healing in the control group.

Time to complete healing

Table 3 summarises the characteristics of the studies that reported time to complete healing. Three studies on PRP gel and one study on L-PRF gel reported time to complete healing. Driver *et al*,[24] Li *et al*[25] and Elsaid *et al*[23] reported a reduction in the meantime to complete healing in the PRP gel group as compared with the control group. Driver *et al*[24] and Li *et al*[25] reported the time in days and Elsaid *et al*[23] in weeks. Goda[20] reported the time for complete closure following L-PRF gel versus control for wound size <10 and >10 cm^2 separately but the data are incomplete such that differences between intervention and control groups cannot be calculated. Among all, none of the studies reported HR (table 3).

Rate of healing

Table 4 summarises the studies that reported the rate of healing per unit time. For PRP gel, Rajendran *et al*[22] reported a higher rate of healing in the intervention

Table 2 Characteristics of the studies for outcome 1: proportion (%) of complete healing

Study ID	Week	Intervention		Control		Risk Ratio* (95% CI)	P value	Certainty of evidence GRADE
		Event n (%)	Total	Event n (%)	Total			
PRP gel								
Rajendran *et al*[22]	6	40 (66.7)	60	0 (0)	60	NR	NR	⊕◯◯◯ Very low
Driver *et al*[24]	12	13 (68.4)	19	9 (42.8)	21	1.6 (0.9 to 2.9)	0.1	
Uçar and Çelik[26]	9	0 (0)	30	0 (0)	30	NR	NR	
Elsaid *et al*[23]	20	3 (25)	12	0 (0)	12	NR	NR	
L-PRF gel								
Somani and Rai[21]	4	5 (55.5)	9	0 (0)	6	NR	NR	

*RR>1 favours intervention.
GRADE, Grading of Recommendations Assessment, Development, and Evaluation; L-PRF, leucocyte-rich and platelet-rich fibrin; PRP, platelet-rich plasma.

Table 3 Characteristics of the studies for outcome 2: time to complete healing

Study ID	Week/day	Intervention Mean/ median SD/IQR	Intervention Total	Control Mean/ median SD/IQR	Control Total	Mean/median difference 95% CI	P value	Certainty of evidence GRADE
PRP gel								⊕◯◯◯ Very low
Driver *et al*[24]	Days (mean)	42.9 (18.3)	19	47.4 (22)	21	−4.5 (−18.9 to 9.3)	0.48	
Li *et al*[25]	Days (median)	36 (30–84)	59	45 (18–60)	58	−9.0 (NR)	0.021	
Elsaid *et al* [23]	Weeks (mean)	6.3 (2.1)	12	10.4 (1.7)	12	−4.1(−5.8 to −2.4)	<0.001	
L-PRF gel								
Goda[20]	Weeks <10 cm^2	4 (NR)	18	6 (NR)	18	NR	NR	
	>10 cm^2	7 (NR)		NR		NR		

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; L-PRF, leucocyte-rich and platelet-rich fibrin; PRP, platelet-rich plasma.

group compared with the control group, while Driver *et al*[24] found little evidence of a difference in the healing rate between treatment and control groups. Li *et al*[25] reported the per cent reduction and not the area per unit of time and published no measures of uncertainty. Regarding L-PRF gel, Goda *et al*[20] again reported the rate of complete healing for wound sizes<10 cm^2 and >10 cm^2 separately. The rate of healing was higher in the intervention compared with control groups for both wound sizes (<10 cm^2 and >10 cm^2). Somani and Rai[21] did not report the summarised data on the rate of healing with L-PRF gel versus control; however, we were able to calculate the average rate of healing in weeks for the study in terms of mean (SD) as the study had provided the data of all the participants for wound healing for each week starting from the baseline (week 0) to the final week

Table 4 Characteristics of the studies for outcome 3: rate of healing per unit time (cm^2 per unit time)

Study ID	Week/day	Intervention Mean SD	Intervention Total	Control Mean SD	Control Total	Mean difference/RR 95% CI	P value	Certainty of evidence GRADE
PRP gel								⊕◯◯◯ Very low
Rajendran *et al*[22]	Week (mean, SD)	5.49 (3.27)	60	0.83 (0.78)	52	4.6 (3.8 to 5.5)	<0.001	
Driver *et al*[24]	Day (mean, SD)	0.051 (NR)	19	0.054 (NR)	21	0.003 (NR)	NR	
Uçar and Çelik[26]	Week (mean, SD)	0.21 (NR)	30	0.018 (NR)	30	0.3 (NR)	NR	
L-PRF gel								
Goda[20]	(%) <10 cm^2 at week 4	100% (NR)	10	68.2% (NR)	11	NR	<0.001	
	>10 cm^2 at week 7	100% (NR)	8	86.8% (NR)	7		0.04	
Somani and Rai[21]	Week (mean, SD)	1.6 (0.9)	9	0.4 (0.2)	6	1.2 (0.6 to 1.9)	<0.001	

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; L-PRF, leucocyte-rich and platelet-rich fibrin; PRP, platelet-rich plasma.

(week 4). The average rate of healing was higher in the intervention group as compared with the control group, with a mean difference of 1.2 cm^2 per week.

Certainty of evidence

Tables 2–4 also summarise the certainty of the evidence for each outcome using the GRADE approach. The certainty of the evidence was found to be very low for all three treatment effects (online supplemental table 7). All treatment effects demonstrated a high risk of bias. These included issues of plausibility in studies where the control group showed a complete lack of healing. The studies listed different end-point types and time points at which observations of complete healing were made. In addition, small sample sizes raised concerns about imprecision.

DISCUSSION

Main findings

This systematic review assessed individual-level RCTs reporting the estimated treatment effects of L-PRF gel and PRP gel on the healing rates in the most common types of skin ulcers: neuropathic ulcers in leprosy and diabetes; and in venous ulcers and pressure ulcers. We found only seven RCTs on surface application of blood products vs standard treatment to promote ulcer healing. Though the point estimates in this review favoured the interventions, the certainty of evidence remains very low. The studies were poorly designed with small sample sizes, a high risk of bias, and provided a lack of comparable data. We note that blinding of participants cannot easily be achieved in studies of blood products unless blood was also collected from control participants. As a result, performance bias is a risk in studies of this type. The highest quality study was conducted by Li *et al*.[25] This study reported two outcomes, time to complete healing and rate of healing, finding a significant difference in favour of the intervention for only the first of these two outcomes. It is unusual to find that no ulcers heal under standard care and this observation in the control groups of four of the five studies reporting proportions healed meant that we could not calculate relative risk ratios. The studies included in this review had reported the findings for a fixed duration of time and did not report the findings beyond the specified period (6 weeks for Rajendran *et al*,[22] 4 weeks for Somani and Rai,[21] 20 weeks for Elsaid *et al*,[23] 2 months for Uçar and Çelik,[26] and 12 weeks for Driver *et al*.[24]) Therefore, when they compared the complete healing between the intervention group and the control group, most of the studies found no healing in the control group suggesting no positive effect of normal saline dressing on wound healing. This in turn also meant that we could not perform a meta-analysis. We considered adding one case to the control group in cases where no healing was recorded but felt that this would not be justified given the poor quality of the studies concerned. Taken in the round, the findings are inconclusive and a large research gap remains.

Treatment effects and standardisation

Across the studies, there were three broad types of treatment effects; time to complete healing, proportion healed at a given time and rate of healing. To further complicate the picture, the proportions healed can be based on different timelines. Only one study, that is, Driver *et al*,[24] included all three outcome observations. Even though Cochrane reviews favour time to complete healing as the main choice of outcome, we included all three types of treatment effects to provide a comprehensive account.[28] Furthermore, different treatment effects have different advantages and disadvantages. For example, rates of healing can provide more precision than other options as multiple observations can be made of the ulcer size over time. Triangulation across multiple treatment effects is a sound approach to scientific understanding. Moreover, the findings for rate of healing differed between different studies for PRP gel (table 4) with Rajendran *et al* showing much higher rates of healing as compared with Uçar and Çelik (5.49 vs 0.21 cm^2/week). The reason why Rajendran showed higher rates of healing is not clear. However, it could be attributed to the initial mean wound size which was larger in the study by Rajendran *et al*.[22] The techniques followed by Rajendran *et al* to prepare PRP gel also differed from the techniques followed by Driver *et al* and Uçar and Çelik.[24 26] The way rate of healing assessed could also have differed. We recommend an attempt to agree to a common standard (or set of standards) for a time cut-off point for the proportion of ulcers completely healed and we recommend that studies record all three generic outcome types above, and also have uniform procedures to prepare L-PRF/PRP gels.

Limitations

Conclusions are severely limited by the nature of the data retrieved, the high risk of biases and the low precision of the studies. The included studies did not uniformly report on all three treatment effects. Even for similar treatment effects, the approaches used for measurement and assessment differed, leading to inconsistency due to a lack of comparable data. Meta-analysis was impossible for reasons described.

In carrying out this study, we followed review guidelines. The inclusion criteria were specific to a single intervention with no overlapping treatment effects and the control group did not include any treatment type other than standard care. This means that our study focused on the specific effect of L-PRF/PRP gel. Though the evidence remains inconclusive, the findings are crucial to highlight the major research gaps. We are attempting to fill this gap with respect to L-PRF gel.[14]

RECOMMENDATIONS

We have recommendations specific to blood product therapies for ulcers and for ulcer care trials in general. Specifically, our findings highlight the importance of further properly designed and well-conducted studies to

generate better evidence. More generally, we think that ulcer studies should include all three measures of effectiveness and that standardisation of cut-off points should be produced. Moreover, multicentre, multicountry studies with uniform procedures to prepare L-PRF/PRP gels and measurement of outcomes, stronger research methodologies to reduce risk of biases, and bigger studies with well-calculated sample sizes to improve precision could provide better and comparable data to generate better evidence.

CONCLUSION

This systematic review showed intervention effects in favour of L-PRF/PRP as follows: a higher proportion of completely healed ulcers in one study, reduced meantime to complete healing in three studies and an improved rate of healing per unit of time in five studies. However, none of these studies were of high quality.

There is a scarcity of studies and the evidence remains inconclusive with poor study design, small sample sizes, high risk of biases and lack of comparable data. Despite the limitations, this systematic review followed robust methods that restricted control procedures to exclude other treatments of unknown effectiveness. Findings show potential for better outcomes in the PRP/L-PRF gel treatment as compared with the standard care. However, the evidence remains inconclusive and highlights a large research gap in ulcer treatment and warrants better designed and methodologically stronger clinical trials with bigger sample sizes to generate stronger evidence.

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Contributors IBN and RJL conceptualised the systematic review. IBN, DS, KN, AA, RD, RK and LG prepared the protocol, performed the screening of the studies, data extraction, risk of bias assessment and data synthesis. OI, PG, SIW, SC and RJL reviewed and revised the manuscript for critically important intellectual content. The overall study was supervised by RJL. All authors reviewed and approved the final version. IBN is the guarantor responsible for overall content.

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Patient consent for publication Not applicable.

Ethics approval Not required as this is a systematic review based on the published literature.

Provenance and peer review Not commissioned; externally peer reviewed.

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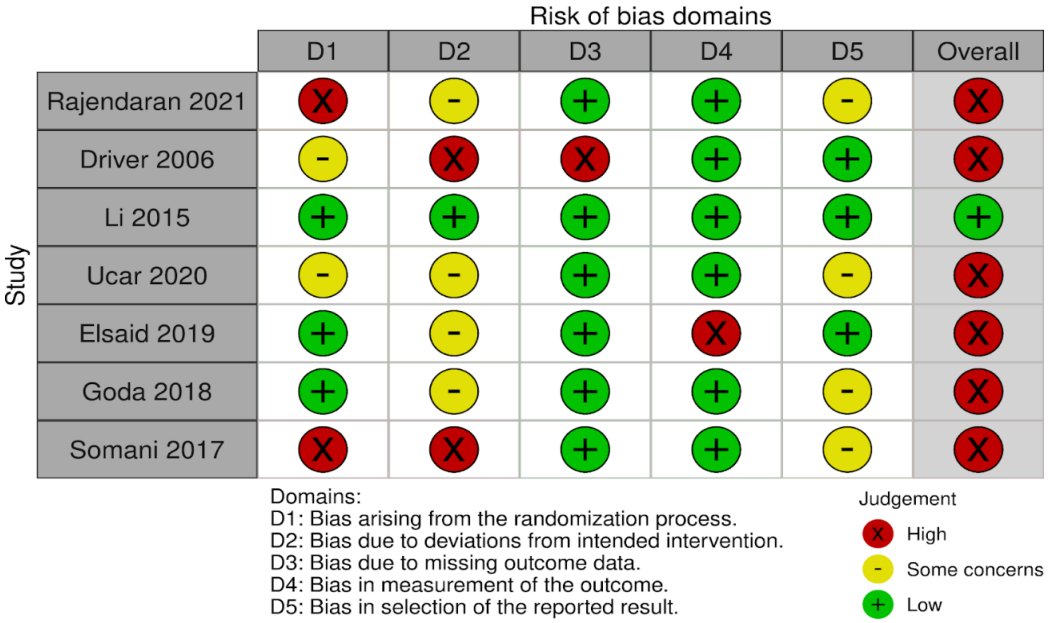
Supplemental Figure 1. Traffic Light Plot of risk of bias of the included studies.



Supplemental Table 1 PRISMA checklist *(page numbers matche with the pdf format)*

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5,6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7, 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8, 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9, 10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9, 10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	10, 11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11-13
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11-13
Study characteristics	17	Cite each included study and present its characteristics.	11-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	16-19
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies.	16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	16-19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not Applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not Applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	16

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	20
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-23
	23b	Discuss any limitations of the evidence included in the review.	22
	23c	Discuss any limitations of the review processes used.	22
	23d	Discuss implications of the results for practice, policy, and future research.	22, 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	29
Competing interests	26	Declare any competing interests of review authors.	29
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

Supplemental Table 2. Search Strategy

OVID Medline		
Search	**Query**	**Items found**
1	"Autologous blood product*".mp.	87
2	L-PRF.mp.	157
3	LPRF.mp.	23
4	"Leucocyte* and Platelet* Rich Fibrin".mp.	33
5	"Leukocyte* and Platelet* Rich Fibrin".mp.	111
6	"Leucocyte*-and Platelet* Rich-Fibrin".mp.	33
7	"Leukocyte*-and Platelet* Rich-Fibrin".mp.	111
8	"Platelet* Rich Fibrin".mp.	1245
9	"Platelet* Rich-Fibrin".mp.	1245
10	"Fibrin, Platelet*-Rich".mp.	11
11	"PRP Gel".mp. (145)	145
12	"Platelet* Rich Plasma Gel".mp.	86
13	"Platelet*-Rich Plasma Gel".mp.	86
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	1523
15	"wound healing".mp.	137033
16	"ulcer healing".mp.	4151
17	15 or 16	139565
18	ulcer*.mp.	257001

19	"Leg ulcer*".mp.	11575
20	"Cutaneous ulcer*".mp.	988
21	"Skin ulcer*".mp.	11100
22	"Pressure Ulcer*".mp.	15061
23	"Decubitus Ulcer*".mp.	1909
24	"Venous Ulcer*".mp.	2357
25	"Varicose ulcer*".mp.	5279
26	"Diabetic Ulcer*".mp.	843
27	"Diabetes ulcer*".mp.	43
28	"Planter Ulcer*".mp.	3
29	"Plantar ulcer*".mp.	537
30	"Foot ulcer*".mp.	7566
31	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	257001
32	14 and 17 and 31	53
33	limit 32 to humans	46
34	"Platelet* Rich Plasma".mp.	
35	"Platelet*-Rich Plasma".mp.	10919
36	PRP.mp.	15750
37	14 or 34 or 35 or 36	22162
38	17 and 31 and 37	223
39	limit 38 to humans	206
OVID Embase		
Search	**Query**	**Items Found**
1	"Autologous Blood product*".mp.	142

2	L-PRF.mp.	236
3	LPRF.mp.	28
4	"Leucocyte* and Platelet* Rich Fibrin".mp.	42
5	"Leukocyte* and Platelet* Rich Fibrin".mp.	147
6	"Leucocyte*- and Platelet* Rich-Fibrin".mp.	42
7	"Leukocyte*- and Platelet* Rich-Fibrin".mp.	147
8	"Platelet* Rich Fibrin".mp.	2089
9	"Platelet*-Rich Fibrin".mp.	2089
10	"Fibrin, Platelet*-Rich".mp.	20
11	"PRP Gel".mp.	223
12	"Platelet* Rich Plasma Gel".mp.	139
13	"Platelet*-Rich Plasma Gel".mp.	139
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	2532
15	"Wound healing".mp.	184510
16	"Ulcer healing".mp.	11918
17	15 or 16	194126
18	Ulcer*.mp.	396201
19	"Leg ulcer*".mp.	16369
20	"Cutaneous Ulcer*".mp.	1574
21	"Skin ulcer*".mp.	21983
22	"Pressure Ulcer*".mp.	11521
23	"Decubitus Ulcer*".mp.	2289
24	"Venous Ulcer*".mp.	3840

25	"Varicose Ulcer*".mp.	600
26	"Diabetic Ulcer*".mp.	1758
27	"Diabetes Ulcer*".mp.	92
28	"Planter ulcer*".mp.	21
29	"Plantar ulcer*".mp.	1082
30	"Foot ulcer*".mp.	13830
31	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	396201
32	PRP.mp.	24885
33	"Platelet* Rich Plasma".mp.	16807
34	"Platelet*-Rich Plasma".mp.	16807
35	14 or 32 or 33 or 34	33903
36	17 and 31 and 35	388
37	limit 36 to human	340
SCOPUS		
Search	**Query**	**Items Found**
1	((TITLE-ABS-KEY ("Autologous blood product*") OR TITLE-ABS-KEY (l-prf) OR TITLE-ABS-KEY (lprf) OR TITLE-ABS-KEY ("Leucocyte* and Platelet* Rich Fibrin") OR TITLE-ABS-KEY ("Leukocyte* and Platelet* Rich Fibrin") OR TITLE-ABS-KEY ("Leucocyte*-and Platelet* Rich Fibrin") OR TITLE-ABS-KEY ("Leukocyte*-and Platelet* Rich Fibrin") OR TITLE-ABS-KEY ("Platelet* Rich Fibrin") OR TITLE-ABS-KEY ("Platelet-Rich Fibrin") OR TITLE-ABS-KEY ("Fibrin, Platelet-Rich") OR TITLE-ABS-KEY (prp) OR TITLE-ABS-KEY ("PRP Gel") OR TITLE-ABS-KEY ("Platelet* Rich Plasma") OR TITLE-ABS-KEY ("Platelet*-Rich Plasma") OR TITLE-ABS-KEY ("Platelet* Rich Plasma Gel") OR TITLE-ABS-KEY ("Platelet*-Rich Plasma Gel"))) AND ((TITLE-ABS-KEY ("Wound healing") OR TITLE-ABS-KEY ("ulcer healing"))) AND ((TITLE-ABS-KEY (ulcer*) OR TITLE-ABS-KEY ("Leg ulcer*") OR TITLE-ABS-KEY ("Cutaneous Ulcer*") OR TITLE-ABS-KEY ("Skin ulcer*") OR TITLE-ABS-KEY ("Pressure ulcer*") OR TITLE-ABS-KEY ("Decubitus ulcer*") OR TITLE-ABS-KEY ("Venous ulcer*") OR TITLE-ABS-KEY ("Varicose ulcer*") OR TITLE-ABS-KEY ("Diabetic ulcer*") OR TITLE-ABS-KEY ("Diabetes Ulcer*") OR TITLE-ABS-KEY ("Planter ulcer*") OR TITLE-ABS-KEY ("Plantar ulcer*") OR TITLE-ABS-KEY ("Foot ulcer*")))	361

CINAHL		
Search	**Query**	**Items Found**
S1	TI “Autologous blood product*” OR AB “Autologous blood product*” OR TI L-PRF OR AB L-PRF OR TI LPRF OR AB LPRF OR TI (“Leucocyte* and Platelet* Rich Fibrin”) OR AB (“Leucocyte* and Platelet* Rich Fibrin”) OR TI (“Leukocyte* and Platelet* Rich Fibrin”) OR AB (“Leukocyte* and Platelet* Rich Fibrin”) OR TI (“Leucocyte*- and Platelet* Rich-Fibrin”) OR AB (“Leucocyte*- and Platelet* Rich-Fibrin”)	104
S2	TI (“Leukocyte*- and Platelet* Rich-Fibrin”) OR AB (“Leukocyte*- and Platelet* Rich-Fibrin”) OR TI “Platelet* Rich Fibrin” OR AB “Platelet* Rich Fibrin” OR TI “Platelet-Rich Fibrin” OR AB “Platelet-Rich Fibrin” OR TI "Fibrin, Platelet-Rich” OR AB "Fibrin, Platelet-Rich” OR TI PRP OR AB PRP OR TI “PRP Gel” OR AB “PRP Gel”	2,781
S3	TI “Platelet* Rich Plasma” OR AB “Platelet* Rich Plasma” OR TI “Platelet*-Rich Plasma” OR AB “Platelet*-Rich Plasma” OR TI “Platelet* Rich Plasma Gel” OR AB “Platelet* Rich Plasma Gel” OR TI “Platelet-Rich Plasma Gel” OR AB “Platelet-Rich Plasma Gel”	2,909
S4	TI “Wound healing” OR AB “Wound healing” OR TI “Ulcer healing” OR AB “Ulcer healing”	15,784
S5	TI Ulcer* OR AB Ulcer* OR TI "Leg Ulcer*" OR AB "Leg Ulcer*" OR TI "Cutaneous Ulcer*" OR AB "Cutaneous Ulcer*" OR TI "Skin Ulcer*" OR AB "Skin Ulcer*" OR TI "Pressure Ulcer*" OR AB "Pressure Ulcer*" OR TI "Decubitus Ulcer*" OR AB "Decubitus Ulcer*"	43,738
S6	TI "Venous Ulcer*" OR AB "Venous Ulcer*" OR TI "Varicose Ulcer*" OR AB "Varicose Ulcer*" OR TI "Diabetic Ulcer*" OR AB "Diabetic Ulcer*" OR TI "Diabetes Ulcer*" OR AB "Diabetes Ulcer*" OR TI "Planter Ulcer*" OR AB "Planter Ulcer*" OR TI "Plantar Ulcer*" OR AB "Plantar Ulcer*"	1,824
S7	TI "Foot Ulcer*" OR AB "Foot Ulcer*"	4,755
S8	S1 OR S2 OR S3	4,112
S9	S5 OR S6 OR S7	43,738
S10	S4 AND S8 AND S9	48
S11	S4 AND S8 AND S9	27
Web of Science		
Search	**Query**	**Items Found**

1	"autologous blood product*" (Title) OR "autologous blood product*" (Abstract) OR L-PRF (Title) OR L-PRF (Abstract) OR LPRF (Title) OR LPRF (Abstract) OR "Leucocyte* and Platelet* Rich Fibrin" (Title) OR "Leucocyte* and Platelet* Rich Fibrin" (Abstract) OR "Leukocyte* and Platelet* Rich Fibrin" (Title) OR "Leukocyte* and Platelet* Rich Fibrin" (Abstract) OR "Leucocyte*-and Platelet* Rich-Fibrin" (Title) OR "Leucocyte*-and Platelet* Rich-Fibrin" (Abstract) OR "Leukocyte*-and Platelet* Rich-Fibrin" (Title) OR "Leukocyte*-and Platelet* Rich-Fibrin" (Abstract) OR "Platelet* Rich Fibrin" (Title) OR "Platelet* Rich Fibrin" (Abstract) OR "Platelet*-Rich Fibrin" (Title) OR "Platelet*-Rich Fibrin" (Abstract) OR "Fibrin, Platelet*-Rich" (Title) OR "Fibrin, Platelet*-Rich" (Abstract) OR "PRP Gel" (Title) OR "PRP Gel" (Abstract) OR "platelet* rich plasma Gel" (Title) OR "platelet* rich plasma Gel" (Abstract) OR "platelet*-rich plasma Gel" (Title) OR "platelet*-rich plasma Gel" (Abstract) OR PRP (Title) OR PRP (Abstract) OR "platelet* rich plasma" (Title) OR "platelet* rich plasma" (Abstract) OR "Platelet*-Rich Plasma" (Title) OR "Platelet*-Rich Plasma" (Abstract)	22762
2	"Wound healing" (Title) OR "Wound healing" (Abstract) OR "Ulcer healing" (Title) OR "Ulcer healing" (Abstract)	83843
3	ulcer* (Title) OR ulcer* (Abstract) OR "leg ulcer*" (Title) OR "leg ulcer*" (Abstract) OR "cutaneous ulcer*" (Title) OR "cutaneous ulcer*" (Abstract) OR "skin ulcer*" (Title) OR "skin ulcer*" (Abstract) OR "pressure ulcer*" (Title) OR "pressure ulcer*" (Abstract) OR "decubitus ulcer*" (Title) OR "decubitus ulcer*" (Abstract) OR "venous ulcer*" (Title) OR "venous ulcer*" (Abstract) OR "varicose ulcer*" (Title) OR "varicose ulcer*" (Abstract) OR "diabetic ulcer*" (Title) OR "diabetic ulcer*" (Abstract) OR "diabetes ulcer*" (Title) OR "diabetes ulcer*" (Abstract) OR "plantar ulcer*" (Title) OR "plantar ulcer*" (Abstract) OR "planter ulcer*" (Title) OR "planter ulcer*" (Abstract) OR "foot ulcer*" (Title) OR "foot ulcer*" (Abstract	181754
4	#1 AND #2 AND #3	149

Supplemental Table 3. Reasons for exclusion

Serial No.	Author	Country	Ulcer type	LPRF/ PRP	Study name	Reason for exclusion
1	Suryanarayan et al (2014)	India	Mixed ulcer	PRP	A study of efficacy of autologous platelet rich plasma in the treatment of chronic diabetic foot ulcers	Non randomized and uncontrolled study
2	Asfia et al (2019)	India	Mixed	PRP	A study on the efficacy of autologous platelet rich fibrin in treatment of chronic non healing leg ulcers	Traumatic ulcer was included
3	Burgos-Alonso et al (2018)	Spain	chronic venous leg ulcers	PRP	Autologous platelet-rich plasma in the treatment of venous leg ulcers in primary care: A randomised controlled, pilot study	waterproof polyurethane dressing (Mepilex) used for control group
4	Amato et al (2019)	Italy	Mixed ulcers	PRP and CGF	CGF treatment of leg ulcers: A randomized controlled trial	Concentrated Growth Factors (CGF) containing gauze and hyaluronic acid was used in both group
5	Rainys et al (2019).	Lithuania.	Mixed ulcers	PRP	Effectiveness of autologous platelet-rich plasma gel in the treatment of hard-to-heal leg ulcers: A randomised control trial	Burn and trauma ulcer were enrolled
6	Escamilla Cardenosa et al (2017)	Spain	venous ulcer	PRGF	Efficacy and safety of the use of platelet-rich plasma to manage venous ulcers	silicon-covered polyamide was used in Intervention group after PRP gel application
7	Li et al (2012)	China	diabetic refractory cutaneous ulcers	PRG	Impact of topical application of autologous platelet-rich gel on medical expenditure and length of stay in hospitals in diabetic patients with refractory cutaneous ulcers	Different outcome
8	Helmy et al (2021)	Egypt	Venous ulcer	PRP	Objective assessment of Platelet-Rich Plasma (PRP) potentiality in the treatment of Chronic leg Ulcer: RCT on 80 patients with Venous ulcer	Intradermal and subdermal injection was done at the edge of the ulcer along with injection of PRP in the granulation tissue of the floor

9	Goda et al (2018)	Egypt	Diabetic foot ulcer	PRP	Platelet-rich plasma for the treatment of diabetic foot ulcer: a randomized, double-blind study	platelet-poor plasma group as a control
10	Bogdan et al (2014)	Belarus	Trophic venous ulcers.	PRP	Prospective randomized clinical trials of efficiency of autologous platelet-derived concentrates to stimulate regeneration of trophic ulcers of venous etiology	PRP injection
11	Semenic et al (2018)	Slovenia	Mixed ulcers	PRP	Regeneration of chronic wounds with allogeneic platelet gel versus hydrogel treatment: A prospective study	local antiseptic was used for dressing and silicone-polyurethane wound dressing was used after PRP, homologous blood was used
12	Joshi et al (2020)	Nepal	leprosy foot ulcer	PRP	Role of platelet-rich plasma in healing diabetic and leprosy foot ulcers in resource-poor setting	We contacted the Author, According to him -This is an ongoing treatment procedure not a research (Conference article only)
13	Kulkarni et al (2019)	India	traumatic and spontaneous ulcer	PRP	Study of efficacy of platelet rich plasma dressing in management of chronic non-healing ulcers	intervention group had PRP injection and traumatic ulcer included

Supplemental Table 4. Summary of the studies in existing systematic reviews on PRP and LPRF that were excluded in our review.

	RCTs included in SRMAs	**Intervention**	**Control**	**Ulcer Type**	**Other published SRMA**								**Reason for exclusion in our SRMA**
	Individual RCTs				**1** Xi 2019	**2** Qu 2020	**3** Chen 2020	**4** Qu 2022	**5** Yan Li 2018	**6** Zhicheng 2018	**7** Lima 2010	**8** Ding 2018	
1	Burgos-Alonso et al (2018)	PRP	SC with additional treatment	Venous	✓	✗	✗	✗	✗	✗	✗	✗	Control group included additional treatment (refer to the supplemental Table 3)
2	Ahmed et al (2017)	PRP	Antiseptic ointment	Diabetic	✓	✓	✗	✓	✓	✓	✗	✓	Control group included antiseptic ointment treatment
3	Escamilla Cardenosa et al (2017)	PRP	SC	Venous	✓	✗	✗	✗	✗	✗	✗	✗	Silicon-covered polyamide was used in the intervention group after PRP gel application (refer to the supplemental file, Table 3)
4	Hersant et al (2017)	SSG +PRP	SSG	Chronic mixed	✓	✗	✗	✗	✗	✗	✗	✗	Overlapping treatment in intervention and control not a standard care

5	Oliveira et al (2017)	PRP	Hypochlorite dressing	Venous	✓	✗	✗	✓	✗	✗	✗	✗	Control not a standard care
6	Volpe et al (2017)	PRP	SC	Diabetic	✓	✗	✗	✗	✗	✗	✗	✗	Intervention group used Cord PRP gel.
7	Karimi et al (2016)	PRP	antiseptic ointment	Diabetic	✓	✓	✗	✗	✗	✗	✗	✗	Control group included antiseptic ointment treatment-not a standard care
8	Raposio et al (2016)	ASC +PRP	SC	Chronic mixed	✓	✗	✗	✗	✗	✗	✗	✗	Overlapping treatments in intervention
9	Saad Setta et al (2011)	PRP	PPP	Diabetic	✓	✓	✗	✗	✓	✗	✗	✓	Control, not standard care
10	Anitua et al (2008)	PRP	SC	Chronic mixed	✓	✗	✗	✓	✗	✗	✗	✗	overlapping treatment in intervention
11	Weed et al (2004)	PRP	PPP	Chronic mixed	✓	✗	✗	✓	✗	✗	✗	✗	Control, not standard care
12	Senet et al (2003)	PRP	SC	Venous	✓	✗	✗	✓	✗	✗	✗	✗	Frozen Autologous Platelet (FAP) suspension in saline solution was used in the intervention group
13	Stacey et al (2000)	PRP	SC	Venous	✓	✗	✗	✓	✗	✗	✓	✗	Intervention group was treated with Platelet lysate, not platelet gel. Placebo is made of

													phosphate buffered solution (PBS)
14	Game et al (2018)	PRP	SC	Diabetic	✗	✓	✓	✗	✗	✗	✗	✗	Standard care plus application of leucopatch in intervention group
15	Gude et al (2019)	PRP	SC	Diabetic	✗	✓	✗	✗	✗	✗	✗	✗	Usual and Customary care with Aurix gel in intervention group
16	Kakagia et al (2007)	PRP	SC	Diabetic	✗	✓	✗	✗	✓	✗	✗	✗	Three groups; none of the group is using standard care.
17	Saldalamacchia et al (2004)	PRP+SC	SC	Diabetic	✗	✓	✗	✓	✓	✓	✓	✓	Overlapping treatment in intervention
18	Singh et al (2018)	PRP	SC	Diabetic	✗	✓	✗	✗	✗	✗	✗	✗	PRP injection with oral antibiotics if required and oral hypoglycemic agents
19	Xie et al (2020)	PRP	SC	Diabetic	✗	✓	✗	✗	✗	✗	✗	✗	Diabetic wound ulcer combined with sinus tract
20	Yang et al (2017)	PRP	SC	Pressure ulcer	✓	✗	✗	✗	✗	✗	✗	✗	Explored the efficacy of intelligent algorithm-based computed tomography (CT) to evaluate platelet-rich plasma (PRP)

													combined with vacuum sealing drainage (VSD)
21	Shreyas et al 2017	PRF	SC	Mixed	✗	✗	✓	✗	✗	✗	✗	✗	Traumatic ulcer also included in cutaneous ulcer
22	Yuvasri et al (2020)	PRF	Unna's paste	Venous	✗	✗	✓	✗	✗	✗	✗	✗	Different control group
23	Amato et al (2019)	CGF	SC	Mixed	✗	✗	✓	✗	✗	✗	✗	✗	Different intervention
24	Santoro et. al (2018)	CGF	Polyurethane film or foam	Vascular	✗	✗	✓	✗	✗	✗	✗	✗	Different control group and conference abstract only.
25	Pravin et al (2016)	PRP	LPRF	Mixed	✗	✗	✓	✗	✗	✗	✗	✗	Different control
26	Steed et al (1992)	HPRP	SC	Diabetic	✗	✗	✗	✓	✗	✓	✗	✗	Homologous PRP-different intervention
27	Steed et. al (1996)	HPRP	Saline gauze	Diabetic	✗	✗	✗	✗	✗	✓	✓	✗	Different intervention group
28	Holloway et al (1993)	HPRP	Placebo	Diabetic	✗	✗	✗	✓	✗	✓	✗	✗	Homologous PRP-different intervention
29	Friese et al (2007)	PRP	Cleaning, polyurethane	Diabetic	✗	✗	✗	✓	✓	✓	✗	✗	Control, not standard care

			foam dressing										
30	Ban et al (2015)	PRP	Standard care	Diabetic	✗	✗	✗	✓	✗	✗	✗	✗	Full article not retrieved
31	Knighton et al (1990)	PRP	Placebo	Mixed	✗	✗	✗	✓	✗	✗	✓	✗	Commercial PRP
32	Krupski et al (1991)	PDWHF	SC	Mixed	✗	✗	✗	✓	✗	✗	✓	✗	Platelet-derived wound healing factors (PDWHF) solution different intervention method (not in a gel form)
33	Moneib et al (2018)	PRP	SC	Venous	✗	✗	✗	✓	✗	✗	✗	✗	Case-control study
34	Serra et al (2013)	APG	No APG	Transmeta-tarsal amputation	✗	✗	✗	✗	✓	✗	✗	✓	Surgical cases
35	Zhang et al (2016)	PRP+SC	SC	Diabetic	✗	✗	✗	✗	✓	✗	✗	✓	overlapping treatment in intervention
36	Zhou et al (2015)	PRP+SC	SC	Mixed	✗	✗	✗	✗	✓	✗	✗	✓	overlapping treatment in intervention
37	Chen et al (2008)	PRP	Skin graft and fibrin glue	Recalcitrant lower extremity ulcer	✗	✗	✗	✗	✓	✗	✗	✓	combination of platelet gel, skin graft and fibrin glue was used
38	Ma et al (2014)	Topical recombinant human acidic fibroblast	Placebo	Deep partial-thickness burn or skin graft donor	✗	✗	✗	✗	✓	✗	✗	✓	Full article not retrieved

		growth factor (rh-aFGF)		sites									
39	Zhu et al (2012)	PRP			✗	✗	✗	✗	✓	✗	✗	✗	Full article not retrieved
40	Liu et al (2016)	APG	Recombinant bovine basic fibroblast growth factor gel	Diabetic	✗	✗	✗	✗	✓	✗	✗	✓	Sinus tract ulcer also included as well as different control group
41	Qi et al (2014)	PRP	SC	Diabetic	✗	✗	✗	✗	✓	✗	✗	✓	Full text not retrieved.
42	Mazzucco et al (2004)	PLT gel	Conventional treatment	Necrotic /dehiscent sternal wounds	✗	✗	✗	✗	✗	✗	✓	✗	Full article not retrieved
43	Crovetti et al (2004)	Platelet gel	Only platelet gel was used	Cutaneous ulcer	✗	✗	✗	✗	✗	✗	✓	✗	Autologous and homologous hemo-component blood were used
44	Ganio et al (1993)	PDWHF or PROCUREN		Diabetic	✗	✗	✗	✗	✗	✗	✓	✗	Full article not retrieved
45	Margolis et al (2001)	Platelet releasate		Diabetic	✗	✗	✗	✗	✗	✗	✓	✗	This is retrospective cohort study
46	Doucette et al (1989)	PDWHF		Diabetic	✗	✗	✗	✗	✗	✗	✓	✗	Full article not retrieved

47	McAleer et al (2006)	Concentrated autologous platelet-derived growth factors	Only concentrated autologous platelet-derived growth factor	Chronic non healing ulcer of lower extremities	✗	✗	✗	✗	✗	✗	✓	✗	Full article not retrieved
48	Keyser et al (1993)	PRP		Diabetic	✗	✗	✗	✗	✗	✗	✓	✗	Retrospective study for control group full text not available (Control group not mentioned in abstract)
49	Glover et al (1997)	CWC plus PR	CWC	Chronic wound	✗	✗	✗	✗	✗	✗	✓	✗	Full article not retrieved
50	Atri et al (1990)	homologous platelet-derived factors and silver sulfadiazine	Normal saline and silver sulfadiazine	Mixed ulcer	✗	✗	✗	✗	✗	✗	✓	✗	Homologous platelets and silver sulfadiazine were used
51	Wang et al (2009)	PRP	Standard care	Refractory diabetic dermal ulcers	✗	✗	✗	✗	✗	✗	✗	✓	Cohort study
52	Wei et al (2008)	PRP		Diabetic	✗	✗	✗	✗	✗	✗	✗	✓	Seminar paper
53	Yan et al (2009)	PRP		Diabetic	✗	✗	✗	✗	✗	✗	✗	✓	Paper not retrieved

Supplemental Table 5. Summary of included studies in this review that were also included in previous reviews

	RCTs included in Systematic review (SR)	**Intervention**	**Control**	**Ulcer Type**	**Our SR**	**Other published Systematic Review and Meta-analysis (SRMA)**							
	Individual RCTs					**1** Xi 2019	**2** Qu 2020	**3** Chen 2020	**4** Qu 2022	**5** Yan Li 2018	**6** Zhicheng 2018	**7** Lima 2010	**8** Ding 2018
1	Driver et al (2006)	PRP	SC	Diabetic	✓	✓	✓	✗	✓	✓	✓	✓	✓
2	Li et al (2015)	PRP	SC	Diabetic	✓	✓	✓	✗	✓	✓	✓	✗	✓
3	Elsaid et al (2019)	PRP	SC	Diabetic	✓	✗	✓	✗	✗	✗	✗	✗	✗
4	Goda et al (2018)	LPRF	SC	Venous	✓	✗	✗	✓	✗	✗	✗	✗	✗
5	Somani et al (2017)	LPRF	SC	Venous	✓	✗	✗	✓	✗	✗	✗	✗	✗

Supplemental Table 6. Summary of included updated studies in this review that were not included in previous reviews.

	RCTs included in Systematic review (SR)	**Intervention**	**Control**	**Ulcer Type**	**Our SR**	**Other published Systematic review and meta-analysis (SRMA)**							
	Individual RCTs					**1** Xi 2019	**2** Qu 2020	**3** Chen 2020	**4** Qu 2022	**5** Yan Li 2018	**6** Zhicheng 2018	**7** Lima 2010	**8** Ding 2018
1	Rajendaran et al (2021)	PRP	SC	diabetic	✓	✗	✗	✗	✗	✗	✗	✗	✗
2	Ucar and Celik (2020)	PRP	SC	pressure	✓	✗	✗	✗	✗	✗	✗	✗	✗

Supplemental Table 7. GRADE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	L-PRF and PRP	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
Proportion of ulcers completely healed											
4	randomised trials	very serious[a]	very serious[b]	serious[c]	extremely serious[d]	none	61/100 (61.0%)	9/99 (9.1%)	**RR 8.26** (0.43 to 159.07)	**660 more per 1,000** (from 52 fewer to 1,000 more)	⊕◯◯◯ Very low
Time of complete healing											
4	randomised trials	very serious[e]	very serious[f]	serious[g]	very serious[h]	none	The mean age range from 40.1 to 61. The sample size range from 12 to 59 in Intervention and control groups among the 4 studies. One study reported (Li) the time of complete healing in median IQR. One study (Elsaid) reported the time of complete healing in months (Mean SD). One study (Driver) reported the time of complete healing in days (Mean SD). One study (Goda) reported the time of complete healing using Cut off time of more less than 10 and more than 10 days.				⊕◯◯◯ Very low
Rate of healing per unit time											
5	randomised trials	very serious[a]	very serious[f]	very serious[g]	very serious[h]	none	Mean age ranged from 39.3 to 64. Sample size ranged from 6 to 60. Rajendaran reported weekly rate of healing in terms of Mean and SD in 0,2 ,4, 6 and average. Driver reported daily rate of healing in Mean days, but SD was missing. Somani reported weekly rate of healing in Mean weeks in 0, 1, 2,3 and 4. Li provided the Grades for rate of healing in proportion.				⊕◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations

a. All studies have overall high risk

b. Heterogeneity is high

c. Leprosy ulcer is not included, majority focused on Diabetic ulcers.

d. Low sample size, high CI

e. All studies except have high risk bias

f. Data is not comparable

g. all participants are older mean age group, most of them were focused on Diabetic Ulcers

h. Small sample sizes