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

Indra B Napit ,[1] Dilip Shrestha,[1] Karuna Neupane,[1] Anju Adhikari,[1] Rolina Dhital,[2] Rachita Koirala,[2] Lovin Gopali,[2] Onaedo Ilozumba,[3] Paramjit Gill,[4] Samuel I Watson ,[5] Sopna Choudhury ,[6] Richard J Lilford [3]

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For numbered affiliations see end of article.

Correspondence to
Dr Indra B Napit;
indran@tlmnepal.org

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.

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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.

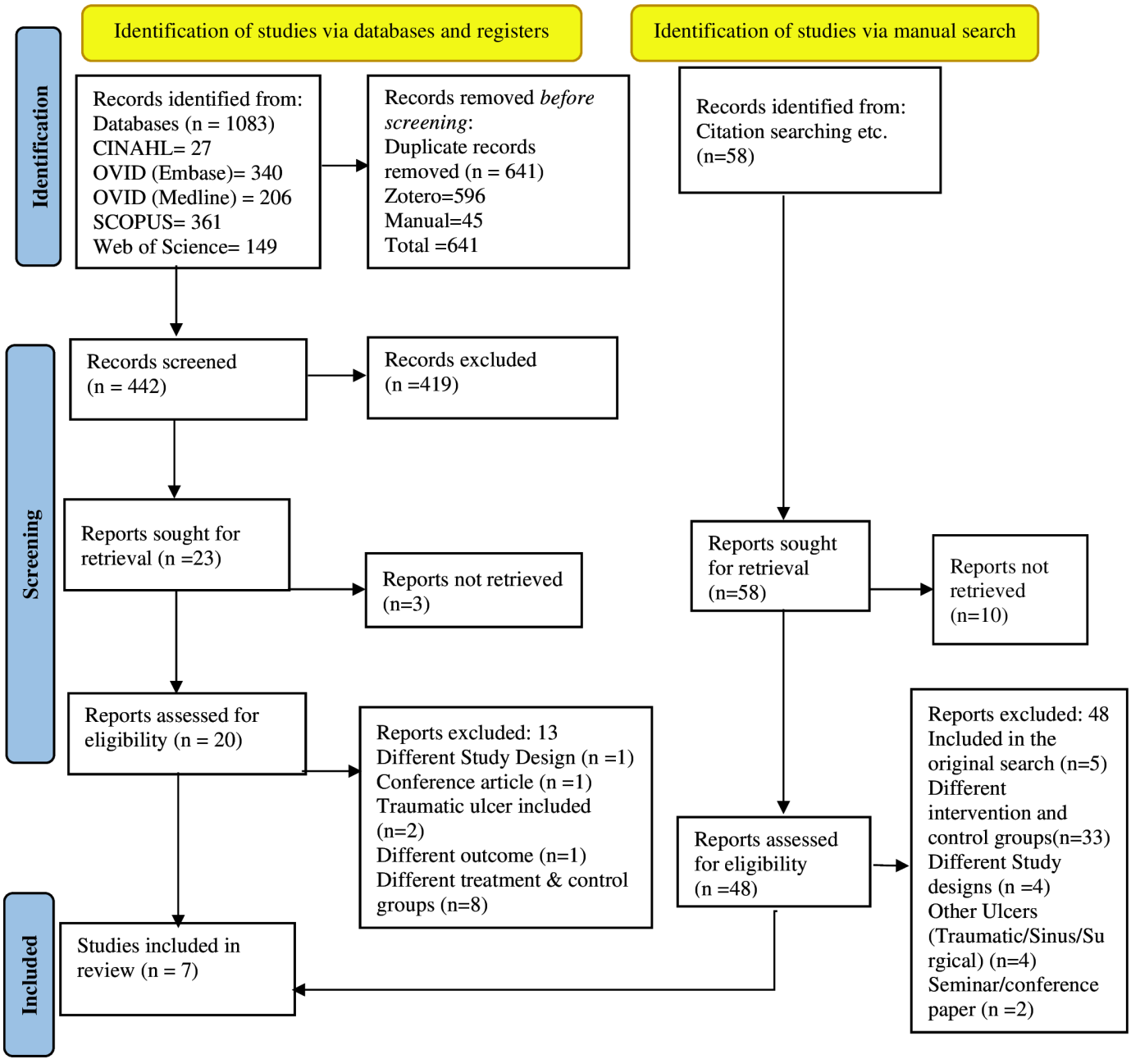

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

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		Control		Mean/median difference 95% CI	P value	Certainty of evidence GRADE
		Mean/ median SD/IQR	Total	Mean/ median SD/IQR	Total			
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		Control		Mean difference/RR 95% CI	P value	Certainty of evidence GRADE
		Mean SD	Total	Mean SD	Total			
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.

Author affiliations
[1]Anandaban Hospital, The Leprosy Mission Nepal, Lalitpur, Nepal
[2]Health Action and Research Pvt Ltd, Kathmandu, Nepal
[3]University of Birmingham, Birmingham, UK
[4]Warwick Medical School, University of Warwick, Coventry, UK
[5]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[6]Institute of Applied Health Research, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK

Twitter Samuel I Watson @siwatson and Richard J Lilford @rjlilford

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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ORCID iDs
Indra B Napit http://orcid.org/0000-0003-0622-880X
Samuel I Watson http://orcid.org/0000-0002-8972-769X
Sopna Choudhury http://orcid.org/0000-0001-5017-6977
Richard J Lilford http://orcid.org/0000-0002-0634-984X

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