Platelet-rich plasma and its utility in medical dermatology: A systematic review

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The field of dermatology has seen numerous therapeutic innovations in the past decade with platelet-rich plasma (PRP), recently garnering significant interest in alopecia, acne scarring, and skin rejuvenation. In other conditions of dermatology, such as chronic wounds and vitiligo, PRP has been investigated but has received less attention. The objective of this literature review was to focus on conditions of medical dermatology and to consolidate the available evidence on PRP for the practicing dermatologist. This review evaluates the literature up to October 31, 2018, and a search was conducted in the PubMed database for "platelet-rich plasma," "platelet releasate," "platelet gel," "platelet-rich fibrin" or "PRP" and "dermatology," "skin," "cutaneous," "wound," or "ulcer." In total, 14 articles met the inclusion criteria for this review. In studies representing Levels of Evidence 1b-4 according to the Centre for Evidence-Based Medicine, Oxford, PRP significantly improved wound healing in chronic diabetic ulcers, venous ulcers, pressure ulcers, leprosy ulcers, acute traumatic wounds, and ulcers of multifactorial etiologies. Two studies also documented benefits of adjunctive PRP in stable vitiligo. In chronic wounds of multiple etiologies and vitiligo, PRP warrants further investigation because it represents a potential therapeutic adjunct or alternative with a favorable side effect profile. (J Am Acad Dermatol 2019;81:834-46.)

Key words: dermatology; platelet-rich plasma; ulcers; vitiligo; wounds.

Platelet-rich plasma (PRP) is a plasma fraction that contains a greater concentration of platelets relative to whole blood, typically 3- to 7-fold the mean platelet concentration of whole blood.[1-3] Platelets contain alpha granules and, upon their activation, secrete growth factors, adhesion molecules, and chemokines that interact with the local environment to promote cell differentiation, proliferation, and regeneration.[4-10]

The production of PRP begins with the collection of 10-60 mL of whole blood on the day of treatment. Anticoagulants, eg, acid citrate dextrose or sodium citrate, are added to prevent ex vivo coagulation and premature secretion of the alpha granules. The blood is then centrifuged to separate cell types based on specific gravity according to Stokes law (Fig 1).

In the single-spin method, the lower portion of the plasma layer is collected as platelet-rich plasma. To increase the platelet concentration of PRP, the plasma and superficial buffy coat are isolated and a second centrifugation can be performed. Dohan Ehrenfest et al defined the methods to isolate leukocyte-rich and leukocyte-poor PRP with the single-spin and 2-spin techniques (Fig 2).[11] For pure PRP (P-PRP), only the most superficial buffy coat is collected with the lower plasma portion, whereas the entire buffy coat is collected in leukocyte-rich PRP (L-PRP).

Calcium or thrombin can be added before administration to create activated autologous PRP, whereas nonactivated autologous PRP can use host dermal collagen and thrombin as endogenous activators. Alternatively, leukocyte- and platelet-rich fibrin (L-PRF) can be produced when the blood is centrifuged without anticoagulant, enabling natural platelet activation and fibrin clot development to ensue before topical application. The variations in processing are important to describe as they affect the structure, growth factor, and cell concentrations of the platelet product (Table I).[12]

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METHODS

The objective of this literature review was to focus on conditions of medical dermatology outside of alopecia, acne scarring, and skin rejuvenation and consolidate the available evidence of PRP for the practicing dermatologist. To identify the evidence up to October 31, 2018, a search was conducted in the PubMed database for "platelet-rich plasma," "platelet releasate," "platelet gel," "platelet-rich fibrin," or "PRP" and "dermatology," "skin," "cutaneous," "wound," or "ulcer." The 547 identified search items were investigated further to include those that specified the method of autologous PRP or PRF preparation and delivery (Fig 3). Given the paucity of large, prospective studies available but also in efforts to limit bias, a sample size of <20 patients and rates of patient dropout >15% were set as exclusion criteria. Other exclusions were nonhuman research, studies not available in English, studies of postsurgical wounds, and studies investigating homologous PRP or other stem-cell products added into the PRP. The reference lists of relevant articles were also searched for potentially appropriate publications. In total, 14 studies investigating ulcers were identified that fulfilled the inclusion criteria. Because of the heterogeneity of studies and widely variable outcome measures, comparison between PRP treatments and subsequent statistical analysis could not be performed. The quality of each individual study was evaluated and levels of evidence were assigned according to the Centre for Evidence-Based Medicine, Oxford.

CAPSULE SUMMARY

- Platelet-rich plasma has garnered interest in alopecia, acne scarring, and skin rejuvenation, but several studies have documented benefits in refractory skin ulcers, as well as vitiligo.
- Activated platelet-rich plasma should be considered as adjunctive therapy to optimize outcomes in vitiligo and skin ulcers refractory to standard wound care.

MEDICAL DERMATOLOGY: ULCERS

Chronic wounds are among the most common medical conditions in the general population, affecting nearly 15% of Medicare beneficiaries with an estimated annual cost of $28-$96 billion (USD).[13] Prior studies have evaluated the role of PRP in chronic ulcer therapy and showed mixed results. Earlier studies are difficult to interpret as the description of the PRP isolation method or delivery technique is often unspecified or ambiguous. Other studies were limited by high rates of patient dropout.[14,15] The current evidence for the use of PRP in medical dermatology is reviewed with focus on the study's quality, the various PRP protocols utilized as well as evaluations of treatment response.

SKIN ULCERS OF MULTIFACTORIAL ETIOLOGY

De Leon et al[16] conducted a large, observational multicenter case series in 200 patients with 285 refractory chronic wounds of a variety of etiologies. Activated autologous P-PRP gel was applied topically once or twice a week. After a mean of 2.8 PRP applications over 2.2 weeks, 86.3% of the wounds responded with an area reduction of 47.5% while 90.5% of the wounds had a 63.6% volume reduction. Specifically, pressure, diabetic, and venous ulcers achieved significantly greater responses than ulcers of other etiologies ($P = .016$).

Pinto et al[17] studied a prospective cohort of 44 patients with lower extremity ulcers recalcitrant to 3 months of standard wound care. Weekly topical autologous L-PRF yielded complete resolution in every patient with small venous ulcers (<10 cm^2), diabetic foot ulcers, or complex multifactorial wounds. Ten of 15 large venous ulcers (>10 cm^2) achieved full closure after a mean of 12.6 treatments. At 3 months, all patients with venous ulcers reported complete alleviation of severe pain that previously required analgesics.

ACUTE TRAUMATIC WOUNDS

Kazakos et al[18] conducted an open-label, randomized, controlled trial of 59 patients with acute traumatic wounds (open fractures, closed fractures with skin necrosis, and frictional burns) not requiring flap coverage. Compared with Vaseline Petrolatum Gauze, topical application of activated autologous undefined PRP (uPRP; unknown if leukocyte rich or leukocyte poor) gel weekly for 3 weeks produced early improvements in wound surface area throughout follow-up starting at week 1 ($P = .003$), as well as lower pain scores at week 2 ($P = .002$) and week 3 ($P < .001$).

CHRONIC DIABETIC ULCERS

Saad Setta et al[19] conducted an open-label, randomized, controlled trial in 21 patients with chronic diabetic ulcers >12 weeks in duration. Patients randomized to twice a week treatment with topical activated autologous L-PRP gel had a faster mean healing time (11.5 weeks) compared with platelet-poor plasma (17 weeks; $P < .005$). Li et al[20] performed a single-blinded, randomized, controlled

Abbreviations used:

CO_2:	carbon dioxide
L-PRF:	leukocyte- and platelet-rich fibrin
NB-UVB:	narrowband ultraviolet B
P-PRP:	pure or leukocyte-poor, platelet-rich plasma
PRF:	platelet-rich fibrin
PRP:	platelet-rich plasma
uPRP:	undefined, platelet-rich plasma

trial of 117 patients with chronic diabetic ulcers. Patients were randomized to either 12 weeks of standard wound care alone or combined with topical activated autologous L-PRP gel every 2 weeks if the wound area had not reduced by ≥80%. In the 12-week treatment period, 39 of 59 (66.1%) required only 1-2 PRP gel treatments, and 20 of 59 (33.9%) required 3-5 treatments. Greater improvements in healing grades ($P < .05$) and time to healing ($P < .05$) were noted with activated platelet gel. Ahmed et al[21] evaluated the role of topical activated autologous L-PRP gel compared with antiseptic iodine ointment dressings in an open-label, controlled trial of 56 diabetic patients with chronic foot ulcers. Treatment was applied twice a week until healing was complete, the occurrence of an infection, or the treatment period ended at 12 weeks. PRP produced greater healing rates at 2 weeks ($P = .003$) and 4 weeks ($P = .044$) than the iodine ointment, but healing rates slowed at 8 weeks; the authors speculated that this reduction could be due to receptor down regulation induced by persistently elevated growth factors. Nevertheless, at 12 weeks, the benefits of PRP use persisted, with higher rates of complete healing (86% vs 68% for controls; $P = .041$) and lower rates of infection ($P = .011$).

Mohammadi et al[22] conducted a prospective cohort study of 70 diabetic patients with chronic diabetic foot ulcers. Topical activated autologous uPRP gel applied weekly for 4 weeks significantly decreased mean ulcer area to 51.9% of baseline ($P = .008$).

Game et al[23] recently published the results of a large, multicenter, single-blinded, randomized controlled trial comparing weekly applications of autologous L-PRF (LeucoPatch, Reapplix, Birkerød, Denmark) to standard wound care in 269 patients with hard-to-heal diabetic foot ulcers. Although 18% of patients dropped out in the per-protocol analysis, we included this study because all of the outcomes were evaluated in the intention-to-treat analysis. In this population, only 3 patients dropped out. At 20 weeks, 34% of the L-PRF group ulcers completely healed versus 22% of ulcers in the standard wound care (odds ratio 1.58, $P = .0235$). Time to healing was significantly shorter ($P = .0246$), and the improvement in ulcer area was significantly greater ($P = .0168$) with the L-PRF treatment.

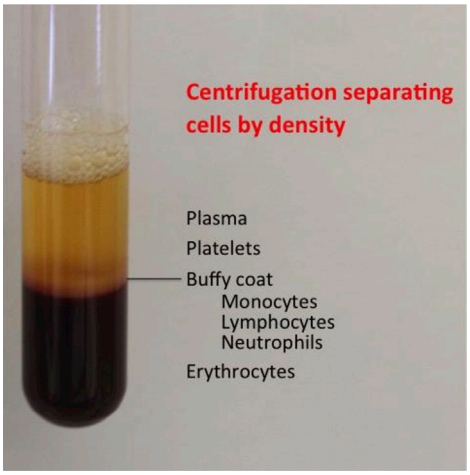

Fig 1. Separation of cell type by specific gravity via centrifugation.

PRESSURE ULCERS

Ramos-Torrecillas et al[24] conducted an open-label, randomized, clinical trial in 100 patients with pressure ulcers for >8 weeks. Patients were randomized to either standard care only, a single dose of topical activated autologous uPRP on day 0, two doses of activated autologous uPRP on day 0 and day 15, or 2 doses of activated autologous uPRP plus hyaluronic acid on day 0 and day 15. At 36 days, ulcer areas were significantly improved in every treatment group when compared with standard care only ($P = .001$). Among the treatment groups, 2 doses of uPRP and hyaluronic acid produced greater healing than 1 dose of uPRP alone ($P \leq .001$). Associations with reduced ulcer healing included statin use ($P \leq .001$) and higher peripheral blood platelet concentration ($P \leq .01$). Two possibilities for this association are excessively elevated local platelet concentrations or PRP's sustained induction of myofibroblast differentiation.[25-27] These findings suggest that an upper therapeutic threshold exists, and further investigation is warranted to identify the most optimal PRP product.

Singh et al[28] performed a prospective cohort study evaluating activated autologous L-PRP gel in the treatment of refractory pressure ulcers in 25 spinal cord injury patients with ≥2 pressure ulcers. One ulcer was treated with biweekly topical activated autologous L-PRP gel and the other with daily saline dressings for 5 weeks. At a mean follow-up of 7 months, activated autologous L-PRP gel treated

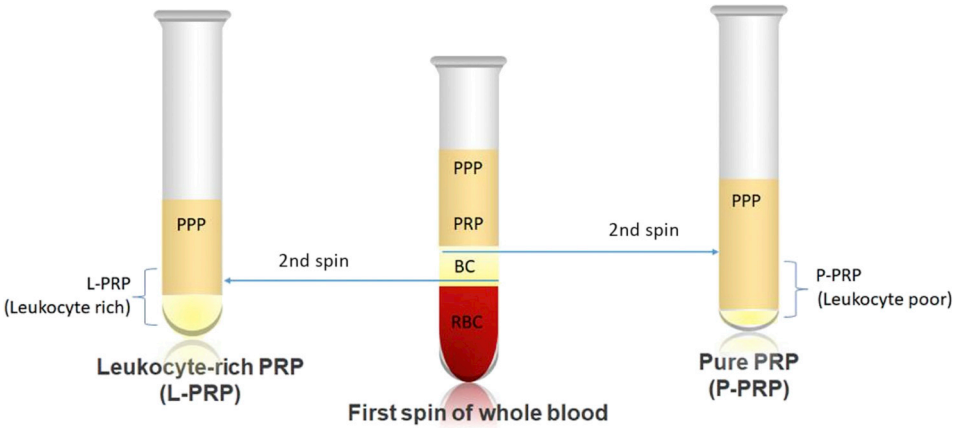

Fig 2. Isolation of P-PRP and L-PRP in a single-spin (softspin) technique or a 2-spin technique. *BC*, Buffy coat; *L-PRP*, leukocyte- and platelet-rich plasma; *PPP*, platelet-poor plasma; *P-PRP*, pure platelet-rich plasma; *PRP*, platelet-rich plasma.

Table I. Differences in platelet-rich products

Platelet product	Anticoagulant	Activation	Fibrinogen polymerization	Fibrin architecture
Platelet-rich plasma	Added before centrifugation	In vivo	Low	None
Activated platelet-rich plasma (or gel)	Added before centrifugation	In vitro activation with Ca^{2+} or thrombin	Low-moderate	Weak
Platelet-rich fibrin	None	In vitro activation without additive	High	Strong

wounds showed a significant reduction in wound surface area from baseline ($P < .001$) unlike saline treated wounds ($P = .924$).

VENOUS ULCERS

Moneib et al[29] performed an open-label, randomized, controlled study in 40 patients with chronic venous leg ulcers of >6 months' duration comparing compression therapy alone to combination with weekly topical activated autologous L-PRP gel for 6 weeks. The activated autologous L-PRP gel significantly improved the mean ulcer area at 6 weeks (67.6% vs 13.7% for controls, $P = .0001$). Complete healing of ulcers was achieved in 35% of patients treated with L-PRP and zero patients in the control group. All patients treated with L-PRP claimed a decrease in the pain, pruritus, and burning associated with the ulcer.

LEPROSY ULCERS

Over 2 million people worldwide experience leprosy complications, including sensory loss, leading to trophic ulcers.[30] PRP might contribute to peripheral nerve regeneration and healing of ulcers secondary to neuropathy.[31-33]

Anandan et al[34] evaluated weekly topical activated autologous L-PRP for a maximum of 6 sessions for neuropathic ulcers in 50 leprosy patients. At the 3-month follow-up, 92% of patients showed complete re-epithelialization within 6 treatment sessions with a mean healing time of 4.38 weeks. There was no association between the rates of wound healing with L-PRP and the patients' spectrum of disease.

STABLE VITILIGO

Ibrahim et al[35] explored the use of activated autologous P-PRP combined with narrowband ultraviolet B phototherapy (NB-UVB) for vitiligo. Sixty patients with symmetric vitiligo stable for >12 months underwent NB-UVB alone on the left side and combination therapy with intradermal activated autologous P-PRP injections was performed on the right side. Patients received phototherapy twice a week and P-PRP injections every 2 weeks for a maximum of 4 months. At 3 months posttreatment, 2 independent dermatologists noted excellent response (>75% repigmentation) in 55% of the lesions treated with P-PRP. In contrast, 75% of the lesions treated with phototherapy alone displayed

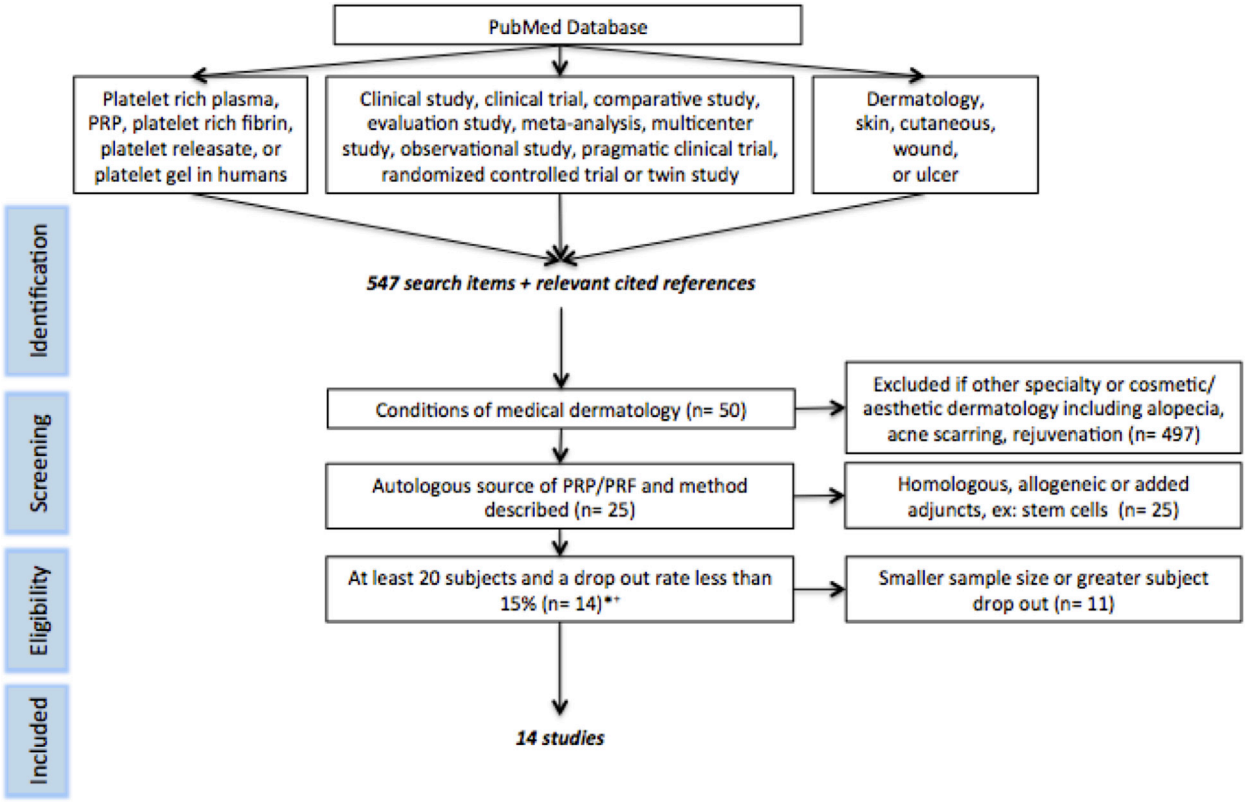

Fig 3. Literature review of platelet-rich plasma in medical dermatology. *Given the paucity of large, prospective studies available but also in efforts to limit bias, a sample site of <20 patients and rates of dropout >15% were set as exclusion criteria. †One included study had a dropout rate of 18% in the per protocol analysis but the objective measurements were evaluated with an intention-to-treat analysis, which included all but 1.25% of recruited patients.

only mild improvement (<25% repigmentation), and none achieved >50% repigmentation ($P < .001$). At 7 months, 50% of the controls showed recurrent depigmentation, while none of the P-PRP—treated lesions relapsed.

Abdelghani et al[36] performed an open-label, prospective, randomized, controlled trial evaluating the efficacy of activated autologous P-PRP, fractional ablative carbon dioxide (CO_2) laser, and NB-UVB in 80 patients with stable vitiligo for 12 months. Patients were randomly assigned to 1 of 4 treatments: fractional CO_2 laser, intradermal activated autologous P-PRP, combination fractional CO_2 laser plus intradermal activated autologous P-PRP, or combination fractional CO_2 laser plus NB-UVB. Three months after the final treatment, evaluations performed by 2 dermatologists blinded to the patients' assigned treatment revealed that combination CO_2 laser plus P-PRP achieved improved repigmentation compared with combination CO_2 laser plus NB-UVB. When combined with CO_2 laser, >75% repigmentation was seen in 40% of P-PRP—treated patients compared with 5% in NB-UVB—treated patients.

Taken together, these studies highlight that PRP, when used adjunctively in combination with NB-UVB or CO_2 laser therapy, can produce better outcomes in treating stable vitiligo. Larger, randomized controlled trials with longer follow-up are required to validate these findings.

DISCUSSION

This review highlights the utility of PRP in treating ulcers of multiple etiologies across 12 studies of a range of Levels of Evidence (1b-4a) including 1051 patients (Table II).[16-24,28,29,34-36] In 10 of 12 reviewed studies, activated PRP was used, and in 2 studies, L-PRF was used. In 6 of 12 studies, L-PRP was investigated, and in 3 studies, uPRP was used. But the only study achieving Level of Evidence 1b utilized autologous L-PRF applied weekly to diabetic foot ulcers.[23] These articles demonstrate that topical activated PRP or autologous L-PRF applied once to twice a week for 3-6 weeks improves wound healing and support a standardized treatment regimen for PRP in chronic ulcers. In addition, symptomatic

Table II. Medical dermatology

Author (year); study design	Study groups	PRP preparation	Outcomes and follow-up	Grade; adverse events
De Leon et al (2011)[16]; large, multicenter, case series of 200 patients with chronic ulcers refractory to standard wound care therapy	The activated autologous P-PRP gel was applied once or twice a week depending on wound characteristics and physician's judgement.	20 mL of blood collected; centrifuged for 60 sec (unknown speed); activator ascorbic acid and calcified thrombin; activated autologous P-PRP gel applied topically to wound	After a mean of 2.8 PRP gel treatments over 2.2 weeks,86.3% of the wounds responded with a reduction of 47.5% in area, 90.5% of the wounds had a 63.6% reduction in volume, 9.5% of the wounds healed completely, and specific wounds achieved significantly greater response: pressure, diabetic, and venous ulcers ($P = .016$). Mean follow-up: 2.2 (0.4-11) weeks.	4; no side effects reported
Pinto et al (2018)[17]; prospective, autocontrolled cohort of 44 patients with leg ulcers refractory to standard wound care for >3 months	Weekly topical application of autologous L-PRF membranes until wound closure. (Compression therapy added for venous leg ulcers, diabetic foot ulcers, and multifactorial wounds.)	9 mL glass-coated plastic tubes without anticoagulant in the IntraSpin system (Intra-Lock International, Boca Raton, FL); 1st spin 2700 rpm × 12 min; autologous L-PRF was gently compressed to obtain 1.0-mm thick membranes	All 17 small venous ulcers (≤10 cm^2, mean baseline area of 4.9 cm^2) reached closure after a mean 6.3 PRP applications; 10/15 large venous ulcers (>10 cm^2, mean area 27.9 cm^2) achieved full closure after a mean 12.6 PRP gel applications; all 10 diabetic foot ulcers reached full closure after a mean 6.8 PRP gel applications. Follow-up: 1 year.	2b; no adverse events recorded

Continued

Table II. Cont'd

Author (year); study design	Study groups	PRP preparation	Outcomes and follow-up	Grade; adverse events
Kazakos et al (2009)[18]; open-label, randomized, controlled trial of 59 patients with acute wounds	1) Conventional therapy of washing wounds, necrotic debridement, and Vaseline gauze dressing every 2 days (32 patients); 2) conventional therapy plus topical activated autologous uPRP gel applied weekly for 3 weeks (27 patients)	Bioteck's PRP Fast system, unknown volume of blood with acid citrate dextrose; 1st spin 3200 rpm × 20 min; activator autologous thrombin at a 10:1 ratio; activated autologous uPRP gel applied topically	Improvements in surface area were statistically greater in the PRP group compared with control at 1 week ($P = .003$), 2 and 3 weeks (both $P < .001$); the control group also displayed significantly higher pain scores at the 2nd and 3rd week ($P = .002$, $P < .001$, respectively). Mean follow-up: 6 (2.5-21) months.	2b; no adverse reactions noted
Saad Setta et al (2011)[19]; open-label, prospective, randomized, controlled trial of 21 diabetic patients with a chronic diabetic ulcer >12 weeks in duration without gangrene or infection	1) Activated autologous L-PRP gel application followed by Vaseline gauze, then dressing twice a week (12 patients); 2) PPP applied followed by Vaseline gauze and dressing twice a week (control, 9 patients)	10 mL of blood with citrate dextrose; 1st spin 1007 g × undefined time; 2nd spin 447 g × undefined time; the lower 20% isolated as L-PRP and the upper 80% as PPP; activator bovine thrombin (0.2 mL per 1 mL PRP) and 10% $CaCl_2$ (0.1 mL)	The mean healing time was 11.5 weeks for PRP patients and 17 weeks for the control ($P < .005$). Follow-up: every 1 week until healed or 20 weeks.	2b; no reported side effects
Li et al (2015)[20]; prospective randomized, controlled, single-blinded trial of 117 patients with refractory diabetic cutaneous ulcers	1) 12-week standard of care (control, 58 patients); 2) 12-week standard of care plus topical application of activated L-PRP gel every 2 weeks if 80% improvement was not achieved (59 patients)	20-100 mL (based on the wound sizes) blood was drawn, with 2-10 mL of anticoagulant (not reported); 1st spin 313 g × 4 min, 2nd spin 1252 g × 6 min; activator thrombin and Ca^{2+} gluconate in a 10:1 ratio	-Number of PRP sessions required to achieve 80% surface area improvement: 1-2 doses for39/59 (66.1%), 3-4 doses for18/59 (30.5%). Kaplan-Meier time-to-healing from ITT population was significantly less in the PRP group at 36 days versus 45 days in the control ($P = .021$). Follow-up: 12 weeks.	2b; no side effects identified

Ahmed et al (2017)[21]; open-labeled, comparative, prospective controlled trial of 56 diabetic patients with a clean chronic nonhealing foot ulcer for >6 weeks and area >2 cm^2	1) Activated autologous L-PRP gel applied twice weekly (28 patients) and 2) antiseptic ointment dressing (28 patients)	20 mL of blood collected; 1st spin 1500 rpm × 5 min; 2nd spin 3500 rpm × 5 min; the pellet was diluted in 3 mL of plasma to make L-PRP; activator 2 mL 10% $CaCl_2$ and 2 mL homologous thrombin; platelet count of PRP gel 1-1.2 × 10^6 platelets/μL	PRP produced a significant increase in number of ulcers healed (P = .003) at 2 weeks and a significantly higher healing rate at 4 weeks (P = .044); at 12 weeks, complete healing seen in 86% compared with 68% of control group (P = .041). The use of the platelet gel showed a lower rate of wound infection (P = .011). Follow-up: 12 weeks.	4; no side effects noted
Mohammadi et al (2017)[22]; prospective cohort of 70 diabetic patients with chronic diabetic foot ulcers	After debridement and washing of the ulcer, 2 mL/cm^2 of activated autologous uPRP followed by a nonabsorbing wet dressing applied weekly for 4 weeks	27 mL of blood with 3 mL of sodium citrate anticoagulant; 1st spin 2000 g × 10 min at 24°C; activator 2 mL of 25 mM $CaCl_2$	At 4 weeks, mean wound area significantly decreased by 51.9% when treated with PRP weekly (P = .008). The correlation between the initial wound area and healed time by week was 0.22 which was not significant (P > .05). Follow-up: 4 weeks	4; no side effects reported
Game et al (2018)[23]; multicenter, international, single-blinded, randomized, controlled trial of 269 patients with diabetes and hard to heal ulcers	Randomized to 1 of 2 groups: 1) standard wound care including off-loading (137 patients) and 2) standard care plus weekly L-PRF application (132 patients)	18 mL of blood drawn into LeucoPatch (Reapplix, Birkerød, Denmark); 1st spin 20 min according to automated programming; L-PRF was placed leukocyte side down onto the ulcer; ulcers >5 cm^2 received 2 patches	In total, 34% of 132 L-PRF group ulcers completely healed vs 22% of 134 ulcers in the standard care group (OR = 1.58, P = .0235). Time to healing was shorter in the L-PRF group (P = .0246).Ulcer area was significantly reduced in the L-PRF group (P = .0168). Follow-up: 26 weeks.	1b; no difference in adverse events

Continued

Table II. Cont'd

Author (year); study design	Study groups	PRP preparation	Outcomes and follow-up	Grade; adverse events
Ramos-Torrecillas et al (2015)[24]; randomized, open-label clinical trial of 100 patients with pressure ulcers >8 weeks, a diameter no larger than 10 cm, showing granulation tissue and no infection or necrosis	1) Standard care only (control, 25 ulcers); 2) 1 dose of activated autologous uPRP on day 0 (34 ulcers); 3) 2 doses of activated autologous uPRP on day 0 and 15 (25 ulcers); 4) 2 doses of activated autologous uPRP + hyaluronic acid on day 0 and 15 (40 ulcers)	20 mL of blood with 3.8% sodium citrate; 1st spin 460 g × 8 min; activator 10% $CaCl_2$ to generate activated autologous uPRP	At 36 days, all 3 treatment groups achieved a significant percent reduction in ulcer area in comparison with the control group ($P \leq .001$). Among the treatment groups, 2 doses of PRP and hyaluronic acid produced greater healing compared with 1 dose of PRP alone ($P \leq .001$). There was no infection noted in any ulcer. Inverse correlations with ulcer healing were seen with statin use ($P \leq .001$) and peripheral blood platelet count ($P \leq .01$). Follow-up: 36 days.	2b; no adverse effects reported
Singh et al (2017)[28]; prospective, self-controlled cohort study of 25 spinal cord injury patients with 2 pressure ulcers, refractory to wound care	For 5 weeks, 1 ulcer was treated with biweekly PRP dressings (activated autologous L-PRP gel, then nonabsorbent Vaseline gauze; control ulcer was treated with daily saline dressings.	30 mL of blood with citrate phosphate dextrose adenine at 1:9 ratio; 1st spin 2000 rpm × 10 min; 2nd spin 2000 rpm × 5 min; activator 10% $CaCl_2$ at 6:1 ratio (PRP, $CaCl_2$)	Activated autologous L-PRP treated wounds had a higher percentage of surface area healed than controls (57.94% vs 2.36%, respectively). Activated autologous L-PRP treated wounds had a significant decrease in wound surface area compared with baseline, unlike control wounds ($P < .001$ vs $P = .924$, respectively). Mean follow-up: 7 months.	4; 4 PRP patients noted declines in hemoglobin

Moneib et al (2017)[29]; open-label, randomized, controlled study of 40 patients with chronic venous leg ulcers <10 cm^2	1) Weekly topical activated autologous L-PRP gel x 6 weeks with compression and dressing (20 patients); 2) conventional compression and dressing x 6 weeks (20 patients, control)	10 mL of blood with acid citrate dextrose; 1st spin 277 g $\times$ 10 min; 2nd spin 277 g $\times$ 5 min; activator 0.1 mL Ca^{2+} gluconate for each 1 mL of PRP	At 6 weeks, improvement in mean ulcer area was significantly greater in PRP versus control (67.6% vs 13.7%, respectively; $P = .0001$); complete ulcer healing was 35% in PRP vs 0% in control. Follow-up: 6 weeks.	2b; no adverse effects noted
Anandan et al. (2016)[34]; prospective, interventional, cohort study of 50 leprosy patients with trophic ulcers	Topical activated autologous L-PRP and occlusive dressings with sterile gauze weekly for a maximum of 6 weeks or until complete ulcer healing	10 mL of blood with acid citrate dextrose at a 10:1.5 ratio; 1st spin 2000 rpm $\times$ 10 min; 2nd spin 3000 rpm $\times$ 10 min; activator 10% $CaCl_2$ at a 10:1 ratio (PRP, $CaCl_2$)	In total, 92% (46/50) of patients showed complete ulcer healing, and88% achieved complete healing within 4 weeks (8% within 3 weeks). Mean time for ulcer healing was 4.38 weeks. Follow up: 6 weeks.	4; no adverse events noted
Ibrahim et al (2016)[35]; open-label, split-side, controlled study of 60 stable vitiligo patients for 12 months	Twice a week NB-UVB on the left side of the body (control side) while the right side was treated with NB-UVB plus intradermal injection of P-PRP every 2 weeks for 4 months or resolution	10-20 mL of blood with sodium citrate (10:1); 1st spin 3000 rpm $\times$ 7 min; 2nd spin 4000 rpm $\times$ 5 min; activator 0.1 mL $CaCl_2$ for each 1 mL of activated autologous P-PRP	After 4 months, 75% of PRP lesions had a good or excellent response ($>$50% repigmentation; compared with 0 controls). At 7 months, the PRP side showed no relapses while 50% of the controls relapsed. Follow-up: 7 months.	2b; injection pain in 50%, bruising in 15%
Abdelghani et al (2017)[36]; prospective, randomized, open-label, comparative study of 80 localized vitiligo patients stable for 12 months	4 treatments: 1) fractional CO_2 laser every 2 weeks; 2) intradermal activated autologous P-PRP every 3 weeks; 3) fractional CO_2 laser, every 2 weeks followed by activated autologous P-PRP 1 week later; 4) fractional CO_2 laser every 2 weeks followed 1 week later with twice weekly NB-UVB	10-20 mL of venous blood was collected in tubes containing sodium citrate as an anticoagulant; 1st spin 252 g $\times$ 10 min; 2nd spin 448 g $\times$ 10 min; P-PRP activated with 0.1 mL of $CaCl_2$ per 0.9 mL of PRP and then injected intradermally	At 3 months after the final treatment, PRP + laser produced the best results, with $>$75% repigmentation in 40% patients and $>$50% repigmentation in 60% patients. There was a significant difference in repigmentation grade and Visual Analogue Scale among the 4 groups ($P = .000$). Follow-up: 5 months.	2b; erythema resolved within 24 hours after laser and NB-UVB

$CaCl_2$, Calcium chloride; *CO_2*, carbon dioxide; *ITT*, intention to treat; *L-PRF*, leukocyte- and platelet-rich fibrin; *L-PRP*, leukocyte- and platelet-rich plasma; *NB-UVB*, narrowband ultraviolet B; *PPP*, platelet-poor plasma; *P-PRP*, pure platelet-rich plasma; *PRP*, platelet-rich plasma; *uPRP*, undefined platelet-rich plasma.

improvement in pain might occur after PRP treatment.[18,29]

The reviewed studies use a wide range of centrifugation speeds limiting the ability to propose an optimal technique for collecting PRP. In vitro, the highest platelet capture efficiency while preserving platelet function was noted with a first spin at 160 g for 10 minutes and a second spin at 250 g for 15 minutes.[37] But an optimal PRP platelet concentration can exist. Fibroblastic proliferation and hyaluronic acid production appear greatest with PRP containing 2−4-fold the peripheral platelet concentration, whereas angiogenesis decreases as platelet concentrations rise above 1.5 million platelets/μL.[38,39]

In this review, we excluded many earlier studies documenting the benefits of PRP obtained from other sources (allogeneic or recombinant) or studies with poorly described methods, studies with poorly described PRP treatments, and studies with higher rates of dropout and selection bias.[14,15,40-45] Recombinant platelet-derived growth factors have been associated with the development of various malignancies in the diabetic population,[46] but this finding has not been reported with autologous PRP. In addition, an autologous source would avoid any potential risk for transmissible diseases or graft-versus-host disease.[47] PRP is generally considered safe but is not without potential risk. A recent report has documented vascular compromise and irreversible blindness after PRP injections for periorbital rejuvenation.[48] This risk is low in the treatment of chronic ulcers and vitiligo because PRP is typically not applied to the face and most studies utilized a topical preparation. Nonetheless, dermatologists should proceed with the appropriate caution and technique during injections of PRP.

There are a variety of advantages that PRP might provide in regards to wound healing. PRP has been shown to display local microbicidal effects.[49-52] PRP also appears to facilitate healing in ulcers, as it alters the matrix metalloproteinase and cytokine expression within 2 weeks after topical application.[53] Although leukocyte inclusion in PRP might contribute to inflammation due to the induction of nuclear factor kappa β,[54,55] in 6 of 12 studies, ulcers were healed with L-PRP. This observation argues against concerns of high concentrations of leukocytes in PRP producing a deleterious inflammatory effect on wound healing. There are no head-to-head studies comparing L-PRP and P-PRP use in ulcers; thus, it is unclear if one preparation is more efficacious. This topic remains an avenue for future investigation.

Recent literature has elucidated the role of platelets in modulating local T-cell immunity through tumor growth factor β.[56] With its proliferative and immunomodulating effects, PRP could be beneficial in T-cell−mediated diseases like vitiligo. We identified 2 studies using adjunctive activated autologous P-PRP in the treatment of stable vitiligo (Level of Evidence 2b).[35,36] In the 140 patients investigated, combining intradermal activated autologous P-PRP injections at 2- to 3-week intervals to CO_2 laser or NB-UVB treatments produced superior outcomes with earlier and more complete repigmentation.

Conclusion

PRP presents an attractive option for treatment-resistant chronic ulcers, which remains a significant economic burden in health care today. With reports of PRP improving symptoms as well as healing rates, it could be considered as adjunctive therapy to minimize the use of systemic medications associated with unfavorable side effect profiles, such as analgesics and opioids. In addition, adjunctive PRP appears to improve repigmentation when treating stable vitiligo.

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