REVIEW

Platelet-rich plasma and its utility in the treatment of acne scars: A systematic review

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The field of dermatology has seen numerous therapeutic innovations in the past decade, with platelet-rich plasma recently garnering significant interest in acne scarring. This review consolidates the available evidence on platelet-rich plasma for the practicing dermatologist and evaluates the current evidence up to May 31, 2018. A search was conducted in the PubMed database for the terms *platelet-rich plasma* or *platelet releasate* or *platelet gel* or *PRP* and *dermatology* or *skin* or *acne* or *scar* or *cutaneous*, with 13 articles meeting the inclusion criteria. The quality of each individual study was evaluated, and levels of evidence were assigned according to the Centre for Evidence-Based Medicine, Oxford, United Kingdom. This review reveals that activated, leukocyte- and platelet-rich plasma in combination with fractional ablative laser treatment administered in 2 or 3 sequential sessions 1 month apart improves the appearance of acne scars. The evidence for the use of platelet-rich plasma with microneedling is less supportive. Because of the heterogeneity of the studies and widely variable outcome measures, comparison between platelet-rich plasma treatments and subsequent statistical analysis could not be performed. Although these studies use various subjective and objective evaluation methods, the addition of platelet-rich plasma provides improvements in acne scarring, higher patient satisfaction, and decreased postprocedure downtime. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2018.11.029.)

Key words: acne; acne scars; dermatology; platelet-rich plasma.

Platelet-rich plasma (PRP) is a plasma fraction that contains a higher concentration of platelets relative to whole blood, typically 3- to 7-fold the mean platelet concentration in whole blood.[1-3] Platelets contain α-granules, and upon their activation, they secrete several growth factors, such as transforming growth factor-β, platelet-derived growth factor, vascular endothelial growth factor, and others.[4-7] These growth factors and other proteins, such as adhesion molecules and chemokines, interact with the local environment to promote cell differentiation, proliferation, and regeneration.[8-10]

The variability in preparation of and terminology related to PRP has brought significant confusion in interpreting the literature. The production of PRP begins with collecting approximately 10 to 60 mL of whole blood on the day of treatment. Anticoagulants, such as acid-citrate-dextrose or sodium citrate, are added to prevent ex vivo coagulation and premature secretion of the α-granules. The whole blood is then centrifuged to separate cell types by specific gravity according to Stokes law (Fig 1).

Abbreviations used:

AA-L-PRP:	activated, leukocyte- and platelet-rich plasma
AA-P-PRP:	activated, pure or leukocyte-poor, platelet-rich plasma
L-PRP:	leukocyte- and platelet-rich plasma
NA-L-PRP:	nonactivated leukocyte- and platelet-rich plasma
PRP:	platelet-rich plasma
TCA:	trichloroacetic acid

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In the single-spin method, the lower portion of the plasma layer is collected as PRP. To increase the platelet concentration of PRP, the plasma and superficial buffy coat can be collected and a second centrifugation can be performed. The resulting platelet pellet can be reconstituted in a portion of the overlying platelet-poor plasma before administration. In efforts to further classify PRP, Dohan Ehrenfest et al, defined the methods to isolate leukocyte-rich and leukocyte-poor PRP by using the single-spin and 2-spin techniques (Fig 2).[11] For the production of pure PRP, only the most superficial buffy coat is collected with the lower plasma portion. When leukocyte-rich PRP is desired, the entire buffy coat is collected with the plasma layer. To induce growth factor secretion, calcium gluconate, calcium chloride, or thrombin can be added before administration (activated PRP). Nonactivated PRP utilizes host dermal collagen and thrombin as endogenous activators. The concentrated platelets remain viable for up to 8 hours.[12]

PRP is generally considered safe, with minimal side effects and few contraindications (Fig 3).

CAPSULE SUMMARY

- Platelet-rich plasma is increasingly being utilized in dermatology for the treatment of acne scars, but the clinical evidence is unclear, with no established standardized protocol.
- Activated, leukocyte- and platelet-rich plasma with a fractional ablative laser administered monthly in 2 to 3 sequential treatments improves acne scarring with less postprocedure downtime.

ACNE SCARRING

Acne vulgaris affects 90% of adolescents; the sequelae of acne scarring can be chronic, leading to associated depression and low self-esteem.[13-18] Scarring is reported in about 95% of acne patients, with 30% developing significant scarring.[19] Atrophic scars, the most commonly observed type, are subdivided into icepick, boxcar, and rolling scars and result from dermal inflammation and overlying skin contraction.[20,21] Grading of atrophic scars as per the Goodman and Baron scale[22] is noted in Figure 4.

Topical retinoids, chemical peels, microdermabrasion, and laser resurfacing have been utilized to induce collagen remodeling and thereby improve the appearance of atrophic scars.[23-29] Limitations of these options include additional scarring, postinflammatory hyperpigmentation, cost, and postprocedure downtime.[30,31] In this article, the current evidence for the use of PRP in the treatment of acne scars is reviewed to assess the quality of the available studies, description of the various PRP protocols, and subjective and objective evaluations of treatment response.

METHODS

A search was conducted in PubMed for the terms *platelet-rich plasma* or *platelet releasate* or *platelet gel* or *PRP* and *dermatology* or *skin* or *acne* or *scar* or *cutaneous*. This search yielded 161 items that we investigated further, including those that specified the method of autologous PRP preparation. Other exclusions were nonhuman research, studies unavailable in English, studies of patients treated with homologous PRP or other stem cell products added to the PRP, and studies having fewer than 10 patients or high rates of subject dropout (>15%). In addition, the reference lists of relevant articles were searched for potentially appropriate publications. A total of 13 articles met the inclusion criteria, with 6 studies (with a total of 210 patients) evaluating PRP combined with microneedling and 7 studies (with a total of 167 patients) evaluating PRP combined with fractional ablative laser therapy (Fig 5). Because of the heterogeneity of the studies and widely variable outcome measures, comparison between PRP-based methods 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, United Kingdom.

MICRONEEDLING AND PRP

Asif et al[32] performed a placebo-controlled, split-face study comparing microneedling alone with combination treatment using activated, leukocyte- and platelet-rich plasma (AA-L-PRP) in 50 patients with acne scars (Goodman severity, 2-4). After microneedling on the entire face, intradermal PRP injection and topical PRP gel were applied on the right side of the face and intradermal injection of distilled water was applied on the left side. Following 3 monthly treatments, improvement in acne scars was noted at a rate of 62.2% in the PRP combination treatment group compared with 45.84% in the control group (P = .00001). Subjectively, almost all patients noted greater reduction in scar visibility with PRP at 3 months ($P < .00001$).

Nofal et al[33] performed a randomized, single-blinded, controlled trial in 45 patients with acne scarring (Goodman severity, 2-4). Patients were

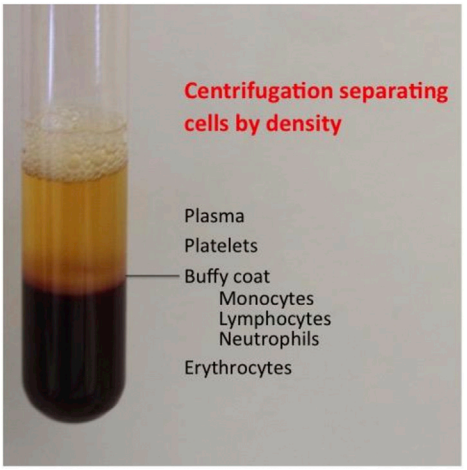

Fig 1. Separation of cell types according to specific gravity via centrifugation.

randomized to 1 of 3 groups undergoing treatment every 2 weeks for 6 weeks with either intradermal activated, pure or leukocyte- and platelet-rich plasma (AA-P-PRP), use of the 100% trichloroacetic acid (TCA) chemical reconstruction of skin scars (CROSS) technique, or microneedling with topical AA-P-PRP. Although all 3 groups showed a significant improvement compared with baseline ($P < .001$), no differences were noted between the 3 groups at 14 weeks.

Ibrahim et al[34] performed a randomized, comparative trial in 90 patients with atrophic scars (Goodman severity, 2-4) from acne, trauma, and varicella. Patients were randomized to 3 groups that received a maximum of 6 sessions of 1 of the following treatments: (1) microneedling alone every 4 weeks, (2) intradermal AA-P-PRP alone every 2 weeks, or (3) alternating microneedling and AA-P-PRP injections every 2 weeks. The greatest improvement in the appearance of acne scars was observed in the group treated with the combination of microneedling and PRP, with the next most significant improvement seen with PRP alone ($P < .001$). Patient satisfaction was also highest in the combination treatment group ($P = .002$).

El-Domyati et al[35] conducted a small randomized, single-blinded, split-face trial in 24 patients with acne scars (severity not reported). Subjects were randomly assigned to a combination of microneedling plus topical AA-L-PRP, combination of microneedling plus TCA 15%, or microneedling alone, with treatments every 2 weeks for a total of 6 sessions. At 3 months, higher mean scar improvement scores were noted in the groups treated with either microneedling plus PRP or microneedling plus TCA 15% than in the group treated with microneedling alone ($P = .015$ and $P = .011$, respectively). However, there was no significant difference between the groups that received a combination treatment ($P = .960$).

Ibrahim et al[36] performed a prospective, single-blinded, split-face clinical trial in 35 patients with mild-to-severe acne scars. All patients underwent 4 treatment sessions at 3-week intervals with microneedling on the right side of the face and microneedling plus topical activated, undefined, platelet-rich plasma (whether it was leukocyte-rich or leukocyte-poor is unknown) on the left side of the face. At 3 months, both the patient satisfaction scores and the evaluations by 2 blinded dermatologists noted significant improvements in both treatment groups when compared with baseline ($P < .001$). Head-to-head, no differences were observed between the 2 treatment groups. Regarding side effects, patients treated with microneedling plus topical PRP experienced less erythema and edema than did those treated with microneedling alone ($P < .001$).

Chawla et al[37] conducted a prospective, split-face, comparative study in 27 patients with acne scarring (Goodman severity, 2-4) comparing 4 treatment sessions of microneedling at 4-week intervals followed by topical activated, undefined, platelet-rich plasma (whether it was leukocyte-rich or leukocyte-poor is unknown) on the right side of the face and microneedling followed by topical 15% vitamin C on the left side. At 4 months, the rates of excellent and good response were not statistically different but patients reported a higher satisfaction score for the PRP-treated side than for the vitamin C–treated side ($P = .01$).

LASER ABLATION AND PRP

Faghihi et al[38] performed a randomized, single-blinded, split-face trial comparing fractional ablative CO_2 laser with combination treatment using AA-L-PRP. A total of 16 patients with predominantly moderate-to-severe rolling and boxcar scars underwent 2 monthly treatments with CO_2 laser ablation followed by injections of AA-L-PRP on 1 half of the face and saline on the other. At 5 months, a trend toward an improved response versus that with saline was noted in the PRP-treated group ($P > .05$). Notably, patients in the PRP-treated group reported greater postprocedure transient erythema and edema ($P < .005$). Lee et al[39] performed a similar study in 14 Korean patients with moderate-to-severe acne scars who underwent 2 monthly treatments of full-face Q-ray ablative fractional CO_2 laser treatment followed by injections of nonactivated, leukocyte- and platelet-rich plasma (NA-L-PRP) on 1 side of the face and saline on the other. In 5 months of follow-up, laser resurfacing–induced erythema improved at

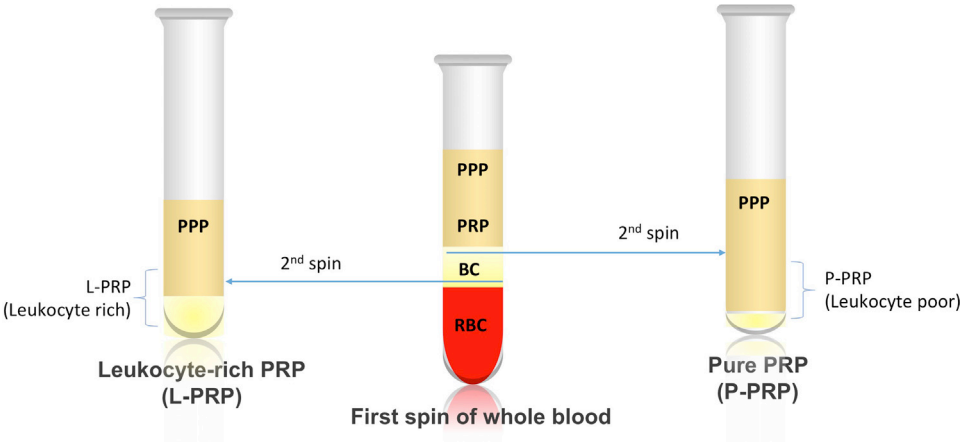

Fig 2. Pure platelet-rich plasma (PRP) versus leukocyte-rich PRP (L-PRP) in a single-spin (soft spin) technique or a 2-spin technique. *BC*, Buffy coat; *PPP*, platelet-poor plasma; *P-PRP*, pure platelet-rich plasma; *RBC*, red blood cells.

Absolute Contraindications	Relative Contraindications
• Critical thrombocytopenia • Platelet dysfunction • Hemodynamic Instability • Sepsis • Local infection at site of PRP administration • Patient unwilling to accept risks	• Nonsteroidal anti-inflammatory drug use within 48 hours • Glucocorticoid injection at treatment site within 1 month • Systemic glucocorticoid use within 2 weeks • Tobacco use • Recent illness or fever • Cancer- especially bone or hematolymphoid • Anemia to hemoglobin < 10 g/dl • Thrombocytopenia to < 105 platelets/μL

Fig 3. Contraindications to platelet-rich plasma (PRP).

a faster rate in the PRP-treated group than in the control group ($P = .01$); the findings were objectively confirmed by using a chromometer ($P = .049$). In the PRP-treated group, the mean duration of erythema, edema, and crusting was significantly shorter ($P < .05$), with a higher degree of clinical improvement in acne scars as judged by blinded evaluators ($P = .03$).

Gawdat et al[40] performed a randomized, split-face, single-blinded, placebo-controlled study of 30 patients with acne scarring (Goodman severity, 2-4). All patients were randomized to 3 monthly sessions of fractional ablative CO_2 laser treatment followed by intradermal AA-L-PRP, topical AA-L-PRP, or intradermal saline. At 6 months, the blinded physician's assessment and patient self-assessment of photographs compared with baseline showed that the groups treated with PRP (topical and intradermal) had significant improvement in skin smoothness relative to that in the areas treated with saline ($P = .03$). No differences were noted between the 2 PRP-treated groups ($P = .10$). Adverse effects, including erythema and edema, were significantly shorter in duration in the PRP-treated groups, leading to shorter downtime ($P = .02$). Kar and Raj[41] performed a similar study using nonactivated, leukocyte- and platelet-rich plasma in 30 patients with atrophic acne scars (Goodman severity, 3 or 4). One month after the final procedure, there was no significant difference in the Goodman and Baron quantitative scores of acne scarring between PRP and the control ($P = .2891$). Patients reported significantly decreased intensity in redness, pain, and swelling on the side treated with PRP compared with the side that received laser treatment alone ($P < .05$).

Min et al[42] performed a prospective, randomized, single-blinded, split-face trial in 25 patients with moderate-to-severe acne scars. All patients underwent 2 monthly sessions of fractional ablative CO_2 laser treatment followed by intradermal AA-L-PRP on 1 side of the face and intradermal saline on the other side. At 2 months after treatment, improvements in acne scarring and patient satisfaction scores were higher in the PRP-treated group than in the saline-treated group ($P < .001$ for the Investigator's Global Assessment scores, $P < .05$ for the Echelle d'évaluation clinique des cicatrices d'acné scores [ECCS], and $P = .016$ for patient satisfaction). Side effects of erythema, swelling, and oozing were significantly lower on the PRP-treated side ($P < .05$). According to quantitative polymerase chain reaction, PRP produced increased expression of epidermal growth factor receptor and a decreased level of keratin 16 in HaCaT cells at 48 hours, lending support to PRP's ability to accelerate postprocedure epithelialization ($P < .05$).

Abdel Aal et al[43] performed a single-blinded, comparative, split-face study in 30 patients with

Grade 1 — Macular erythematous hypo- or hyperpigmented scars

Grade 2 — Mild atrophy not obvious at social distances of >50 cm or easily covered by facial make up or beard hair.

Grade 3 — Moderate atrophy obvious at social distance of >50 cm; not easily covered by make up or beard hair; but able to be flattened by manual stretching

Grade 4 — Severe atrophy not flattened by manual stretching of skin.

Fig 4. Goodman and Baron scale.

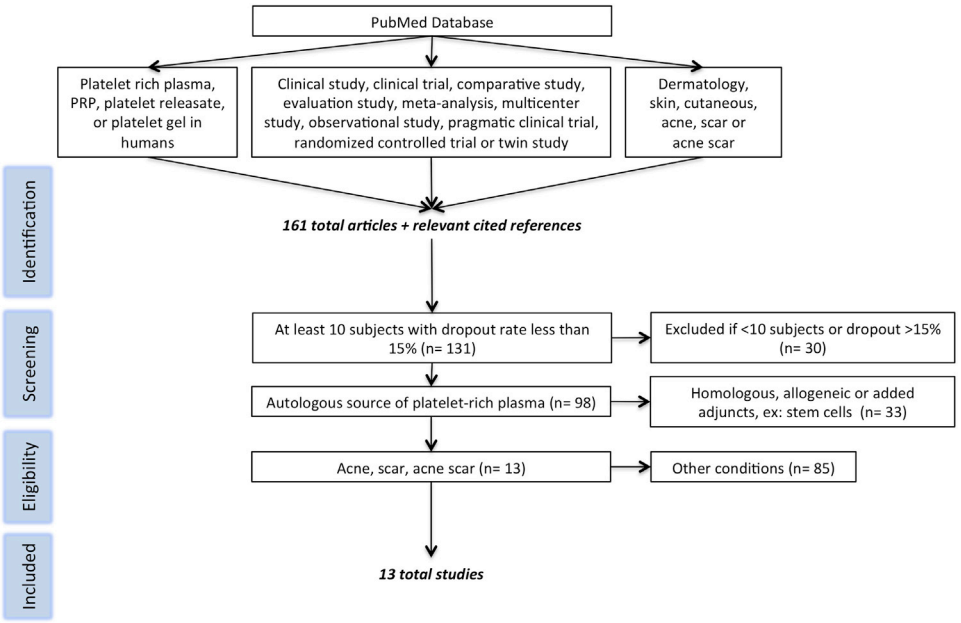

Fig 5. Review of the literature on acne scarring. *PRP*, Platelet-rich plasma.

mild-to-severe acne scarring. Patients were treated with a fractional ablative CO_2 laser followed by intradermal AA-L-PRP injections to just the right half of the face in 2 treatment sessions with a 3- to 4-week interval. Blinded evaluation by 2 dermatologists at the 6-month follow-up showed significantly improved appearance of acne scars in the combination treatment group compared with the group that received CO_2 laser monotherapy ($P < .001$). Higher patient satisfaction was seen with combination treatment ($P < .001$). Postprocedure erythema was noted with both therapies but was shorter in duration after combination therapy ($P = .0052$).

Zhu et al[44] evaluated the use of topical AA-L-PRP in conjunction with a fractional ablative erbium laser treatment for the treatment of acne scarring. In all, 22 patients with moderate-to-severe acne scars received 3 laser treatments that were administered 1 to 2 months apart and followed by topical AA-L-PRP. Two blinded dermatologists noted moderate clinical improvement at 4 weeks after treatment. The physicians' assessment yielded ratings of excellent or markedly improved in 68% of patients, and no patient was rated as being without improvement. The patients' assessment showed that 91% were satisfied or very satisfied, with 45% wanting to receive further treatment.

DISCUSSION

In this review of the literature to date, PRP has been studied as an adjunctive therapy to microneedling or fractional ablative laser. A total of 13 studies representing levels of evidence 2b to 4 evaluated the use of PRP in a total of 377 subjects with acne scarring.

The microneedling studies utilize activated PRP prepared by using a 2-spin centrifugation technique with an initial collection volume of 10 to 20 mL of

Table I. PRP with microneedling

Study design	Study groups	PRP preparation	Outcomes and follow-up	Level of evidence and adverse events
Asif et al (2016)[32] Prospective, placebo-controlled, split-face study 50 patients (mean age, 25.7 y) with Fitzpatrick skin types III-V and Goodman severity 2-4	3 monthly sessions of microneedling with intradermal injection and topical application: (1) AA-L-PRP on the right side of the face (2) Distilled water on the left side of the face	- 17 mL of blood was collected in a 20-mL syringe containing 3 mL of acid-citrate-dextrose - First spin, 293.8 $g \times 5$ min - Second spin, 690.94 $g \times 17$ min - Activator, 10% calcium chloride (0.2 mL with 2 mL of PRP) - Full-face microneedling to 1.5 mm - 1 mL of AA-L-PRP was injected intradermally, 0.1 mL/cm^2 into the right half of the face; the remaining 1 mL of PRP was allowed to form a platelet gel, and the supernatant fluid and gel were applied topically - The left side of the face was injected with distilled water intradermally - Mean PRP platelet concentration, 1.17 $\times$ 10^6/μL, 5-fold higher than the concentration from whole blood	3 mo after treatment, - The halves treated with PRP and distilled water showed 62.20% and 45.84% improvement, respectively, on the Goodman quantitative scale ($P < .00001$) - According to the Goodman qualitative scale, the PRP-treated side showed excellent response in 20 patients (40%) and good response in 30 (60%), whereas the distilled water–treated half of the face showed excellent response in 5 patients (10%), good response in 42 patients (6%), and poor response in 3 patients ($P < .00001$) Subjectively, almost all patients claimed that PRP provided greater reduction in visibility of scars than did distilled water at study completion ($P < .00001$) Follow-up, 3 mo	4 Acne flare rate, 4% PIH rate, 8% Milia rate, 2% Persistent erythema rate 2% Bruising rate, 4%
Nofal et al (2014)[33] Prospective, randomized, controlled trial 45 patients (mean age, 25 y) with Fitzpatrick skin types III-V and Goodman severity 2-4 were randomized to 3 equal groups	3 sessions at 2-wk intervals: (1) Intradermal injection of AA-P-PRP: 0.1-0.3 mL of PRP was injected intradermally into the atrophic scars by using an insulin syringe, with a total of 1 mL of PRP in each side of the face (2) TCA 100% was applied focally on the scars by	- 10 mL of blood was collected in tubes containing trisodium citrate - First spin, 150-200 $g \times 10$ min - Second spin, 1500-2000 $g \times 15$ min - A portion of the PPP was used to resuspend the platelets to produce 2 mL of P-PRP - Activator, 10% calcium chloride (0.1 mL per 0.9 mL of PRP)	At 14 wk, there was no statistical difference in improvement of qualitative global scarring grades between the 3 groups; no significant difference in the quartile grading scale or patient satisfaction was noted No significant correlations with response were found in any of the 3 groups Follow-up, 14 wk	4 Only periprocedural pain was reported in all patients No other adverse effects were noted

	using a cotton-tipped wooden applicator until frosting occurred, usually within 10 s (3) AA-PRP and microneedling (topical 0.5-1 mL of PRP was applied to the face, followed by microneedling to 2 mm)			
Ibrahim et al (2017)[34] Prospective, randomized, controlled trial 90 patients (mean age, 26.3 y) with Fitzpatrick skin type II-IV and Goodman severity 2-4 Atrophic scars from acne, trauma, and varicella	For a maximum of 6 sessions: (1) Microneedling (using a dermapen with 9 microneedles with a length of 0.25-2.5 mm), 1 session every 4 wk (28 patients) (2) Intradermal AA-P-PRP injection every 2 wk (34 patients) (3) Alternating sessions of microneedling and AA-P-PRP every 2 wk (18 patients)	- 10-20 mL of blood was collected into a sodium citrate (10:1) tube - First spin, 1419 $g \times 7$ min - Second spin, 2522 $g \times 5$ min - The lower 1-2 mL of plasma yielded the PRP - Activator, CaCl (10:1) added to P-PRP; intradermal/subcutaneous injections into scars at 0.1 mL per scar and with a space of 1 cm between injections in linear post-traumatic scars	3 mo after the final treatment, a significant difference in mean improvement in acne scarring was noted between the groups: the highest response was with the combination of microneedling and PRP (70.43%), followed by with PRP alone (48.82%) and lastly with microneedling alone (39.71%) ($P < .001$) Patient satisfaction was highest with the combination of microneedling and PRP vs with PRP or with microneedling alone ($P = .002$) Nonacne scars responded better than acne scars to PRP alone ($P = .001$) and PRP plus microneedling ($P = .023$) In the group treated with PRP alone, boxcar and icepick scars responded better than rolling scars ($P = .028$) Follow-up, 3 mo following the final treatment	2b Pain ratings were noted as most severe with microneedling alone, then with microneedling and PRP and lowest with PRP alone ($P < .001$) Erythema was more severe with a combination of microneedling and PRP, followed by with microneedling alone (patients in the combination group had lighter skin)

Continued

Table I. Cont'd

Study design	Study groups	PRP preparation	Outcomes and follow-up	Level of evidence and adverse events
El-Domyati et al (2018)[35] Prospective, single-blinded, randomized, split-face trial 24 patients (mean age, 27.3 y) with Fitzpatrick skin type III or IV; acne severity was not reported	Treatments every 2 wk for 6 sessions: (1) Combination of microneedling and topical AA-L-PRP on the right side of the face and microneedling alone on the left side of the face (8 patients) (2) Combination of microneedling and TCA 15% on the left side of the face with microneedling alone on the right side of the face (3) Combination of microneedling and topical AA-L-PRP on the right side of the face and microneedling and TCA 15% on the left side of the face	- 10 mL of blood was collected into tubes containing 2 mL of acid-citrate-dextrose (2:8) - First spin, 252 $g \times 10$ min - Second spin, 1792 $g \times 5$ min - The lower one-third of the supernatant with platelet pellet was used as PRP - Activator, calcium gluconate in a 1:9 ratio - PRP was applied topically for 5 min after microneedling to 1.5 mm TCA 15% was applied with a cotton-tipped applicator until even white frosting was seen	At 3 mo, - There was a significantly higher mean improvement in scar score with the microneedling and PRP combination (64.87) vs with microneedling alone (29.12) ($P = .015$) - There was a significantly greater mean improvement in score with the microneedling and TCA 15% combination (81.87) than with microneedling alone (61.87) ($P = .011$) - There was no significant difference between microneedling plus TCA 15% and microneedling plus PRP ($P = .960$) - Histologically, the mean epidermal thickness increased significantly after 3 mo in all treatment groups ($P < .05$) - Microneedling plus PRP was more effective than microneedling alone ($P = .032$) - The combination of microneedling plus TCA 15% was more effective than microneedling alone ($P = .002$) - No difference between microneedling plus PRP and microneedling plus TCA 15% ($P = .843$) Follow-up, 3 mo	2b Erythema that resolved in 1-2 d was reported in all groups No other adverse events were noted

Ibrahim et al (2018)[36] Single-blinded, split-face, prospective clinical trial 35 patients (mean age, 24.7 y) with Fitzpatrick skin type I-IV and mild-to-severe acne scars	4 treatments at 3-wk intervals: (1) Microneedling followed by topical AA-uPRP on the left side of the face (2) Microneedling	- 10 mL of blood was collected in tubes with acid-citrate-dextrose - First spin, 2500 rpm × 10 min - Second spin, 3500 rpm × 10 min - PPP was partly used to resuspend the platelets - Activator, Ca gluconate (with PRP in a ratio of 1:9) - Microneedling to 1.5 mm	Grading according to the qualitative global acne scarring system of Goodman and Baron by 2 blinded dermatologists 3 mo after treatment - Significant improvement in the degree of scar severity before and after treatment on both sides of the face ($P < .001$) - No significant difference between the 2 sides after treatment Patient satisfaction scores were significantly higher after both treatments, but no significant difference between the 2 groups was noted ($P = .073$) Follow-up, 12 mo	4 Significantly less erythema and edema with microneedling plus PRP (4.3 d) and (1.9 d), respectively, versus with microneedling alone (6.2 d) and (3.3 d) ($P < .001$)
Chawla et al (2014)[37] A prospective, split face, comparative study 27 patients (mean age, 27.5 y) with a Goodman severity of 2-4	4 treatments with an interval of 4 wk between sessions (1) Microneedling with topical AA-uPRP on the right side of the face (2) Microneedling with topical vitamin C 15% on the left side of the face	- 10 mL of blood was collected in tubes with acid-citrate-dextrose - First spin, 1500 rpm × 10 min - Second spin, 3700 rpm × 10 min - The mean PRP platelet count was 8-9 × $10^5/\mu$L, which was 4.5× that of peripheral blood - Activator, Ca gluconate, was added (in a ratio of 1:9) - 2 mL of AA-uPRP as used per treatment - Microneedling to 1.5 mm	At 4 mo, a poor response rate was seen in 22.2% of those treated with PRP and 37% of those treated with vitamin C ($P = .021$) Patient satisfaction was greater with PRP ($P = .01$) Follow-up, 4 mo	4 No adverse events were reported

AA-L-PRP, Activated, leukocyte- and platelet-rich plasma; *AA-P-PRP*, activated, pure or leukocyte-poor, platelet-rich plasma; *AA-PRP*, activated, platelet-rich plasma; *AA-uPRP*, activated, undefined, platelet-rich plasma (whether it was leukocyte-rich or leukocyte-poor is unknown); *PIH*, postinflamatory hyperpigmentation; *PPP*, platelet-poor plasma; *pPRP*, pure platelet-rich plasma; *PRP*, platelet-rich plasma; *TCA*, trichloroacetic acid.

Table II. PRP with laser ablation

Study design	Study groups	PRP preparation	Outcomes and follow-up	Level of evidence and adverse events
Faghihi et al (2016)[38] Randomized, single-blinded, placebo controlled, split-face study 16 patients (mean age, 36.8) with Fitzpatrick skin types II-IV with moderate-to-severe facial atrophic acne scars, predominantly rolling and boxcar types with <20% of the icepick type	2 treatments, 1 mo apart: Both cheeks treated with ablative CO_2 laser (Q-ray; energy, 30 mJ, pixel pitch, 1; and depth, 600 μm) After the ablation, each side of the face was randomly assigned to either (1) intradermal AA-L-PRP or (2) Saline	- 20 mL of blood was collected in a tube with 2.4 mL of citrate-phosphate-dextrose - First spin, 2000 g × 3 min - Second spin, 5000 g × 5 min - Platelet pellet mixed with 4 mL of supernatant producing 4 mL of L-PRP - Activator, 3% CaCl, which was added to make 4 mL of AA-L-PRP - Intradermal injections of 0.2 mL were made within 2-cm intervals	Serial photography was evaluated by 2 blinded dermatologists on a quartile grading scale: - At 1 mo, a fair or good response was noted at a rate of 68% with PRP treatment and 50% on the saline-treated side (P = .15) - Patients noted being satisfied or very satisfied with the PRP treatment in 50% of cases and with saline in 31.2% of cases (P = .18) - At 5 mo, a fair or good response with PRP was seen in 87.5% of cases and with saline in 68.8% of cases (P = .23); no patients had an excellent outcome - Patients noted being satisfied or very satisfied with the PRP treatment in 56.2% of cases and with the saline treatment in 43.8% of cases (P = .12) Follow-up, 5 mo	2b More erythema with PRP on d 0, d 2, and d 4 (P = .003, P = .007, P = .004, respectively) More edema with PRP on d 0, d 2, and d 8 (P = .003, P = .004, P = .004, respectively) No other side effects
Lee et al (2011)[39] A randomized, prospective, single-blinded, placebo-controlled, split-face trial 14 Korean patients (mean age, 28.1 y) with Fitzpatrick skin type III-V and moderate-to-severe acne scars	2 sessions performed 1 mo apart Entire face treated with a Q-ray ablative fractional CO_2 laser (pulse energy, 25 mJ per fixed 150-μm-diameter microbeam and a density of 400 MTZ/cm^2) followed by (1) NA-L-PRP injections on 1 half of the face (2) Saline injections on the other half	- In Prosys PRP system (Prodizen, Seoul, South Korea), 60 mL of blood was collected into a syringe with anticoagulant (not reported) in a ratio of 1:10 - First spin, 3000 rpm × 3 min - Second spin, 4000 rpm × 3 min - 6 mL of NA-L-PRP was produced and injected at 20 individual sites on 1 side of the face at 1.5- to 2-cm intervals, with each site receiving 0.3 mL of NA-L-PRP or normal saline	2 blinded dermatologists evaluated clinical improvement in acne scars at 5 mo as follows: - The overall degree of clinical improvement was significantly better on the PRP-treated side (2.7) than on the saline-treated side (2.3) (P = .03) Erythema measured by a CR-400 Chroma Meter (Konica Minolta, Tokyo, Japan): - Erythema on the PRP-treated side improved faster than on the saline-treated side and was significantly less at d 4 (P = .01), as confirmed with the chromometer (P = .049) The mean duration of erythema was 10.4 d on the saline-treated side vs 8.6 d on the PRP-treated side (P = .047) The mean duration of edema was 7.1 d on the saline-treated side vs 6.1 d on the PRP-treated side (P = .04) Mean duration of post-treatment crusting was 6.8 d on the saline-treated side vs 5.9 d on the PRP-treated side (P = .04) Follow-up, 5 mo	2b No other adverse effects observed

Gawdat et al (2014)[40] Randomized, split-face, single-blinded, placebo-controlled study 30 patients (mean age, 24.8 y) with Fitzpatrick skin III-V with atrophic scars having a Goodman severity of 2-4	3 monthly sessions of fractional CO_2 laser (Smartxide DOT [Deka, Calinzano, Italy] with power, 15 W; dwell time, 600 μs; spacing, 700 μm; smart stack, level 2) followed by either (1) Intradermal AA-L-PRP on 1 side and intradermal saline on the other (15 patients) or (2) Intradermal AA-L-PRP on 1 side and topical AA-L-PRP on the other (15 patients)	- 10 mL of blood was drawn into a syringe with 1.5 mL of acid-citrate-dextrose - First spin, 150 $g \times 15$ min - Second spin, 400 $g \times 10$ min - Pellet of platelets was mixed with 1.5 mL of supernatant to make 1.5 mL of L-PRP - Activator, 1 mL of 3% CaCl - Injections of 0.2 mL administered at 10 different sites approximately 1.5 cm apart	Photographs at baseline and 6 mo were evaluated by a blinded physician using a 4-point scale as follows: - Areas treated using either the intradermal or topical PRP showed significantly more improvement in skin smoothness than did the saline-treated area ($P = .03$) - No significant improvement was noted between intradermal PRP and topical PRP ($P = .10$) Excellent response was noted with intradermal PRP (66.7%), which was more effective than topical PRP (60%), which was more effective than saline (26.7%) (no P value was reported) OCT to measure depth of acne scars with an RTVue-100 OCT tomopgraph (Optovue, Fremont, CA) showed improvement in scar depth with intradermal and topical PRP treatment than with saline treatment ($P = .01$) At 9-mo follow-up, continued improvement seen in all areas but clinically more obvious in areas treated with intradermal or topical PRP than with saline Follow-up, 6 mo (all patients); 9 mo (in 13 patients)	2b Erythema, edema, mild crusting, PIH, and acne eruption all had significantly shorter duration in areas treated with PRP, leading to significantly shorter downtime ($P = .02$) Periprocedural pain was significantly greater with intradermal PRP than with topical PRP or intradermal saline ($P = .005$)
Kar and Raj (2017)[41] A prospective, single-blinded, split face, comparative study 30 patients (mean age, 25.06 y) with Fitzpatrick skin type III-V and Goodman severity of 3-4	3 monthly treatment sessions with a fractional CO_2 (area, 2 cm^2; density, 0.8 mm; pulse width, 1540 μs; overlap 6-8; energy 200-250 mJ) as follows: - Fractional ablative CO_2 laser treatment on the right side of the face - Combination therapy consisting of fractional ablative CO_2 treatment with topical NA-L-PRP on the left side	- 10 mL of whole blood was drawn and transferred to a vial containing an unspecified anticoagulant - First spin, 1500 rpm $\times$ 10 min - Second spin, 3000 rpm $\times$ 20 min - L-PRP was collected for topical application immediately following the CO_2 laser treatment	Evaluated by an independent observer 1 mo after final treatment by using the Goodman and Baron quantitative scale - Appearance of acne scars on both the right and left sides of the face was significantly improved compared with baseline ($P = .0001$) - No significant difference in the appearance of scars between the right and left sides of the face ($P = .2891$) - Patients' self-assessment scores for the quality of scars were significantly higher for both treatment sides compared with baseline ($P = .0001$) - Patients reported significantly decreased intensity of erythema, edema, and pain symptoms on the side treated with combination treatment including topical PRP compared with laser treatment alone ($P < .05$) Follow-up, 3 mo	4 3 patients were lost to follow-up, 1 patient stopped early because she became pregnant, and 2 patients discontinued the study because of downtime and side effects

Continued

Table II. Cont'd

Study design	Study groups	PRP preparation	Outcomes and follow-up	Level of evidence and adverse events
Min et al (2018)[42] A prospective, single-blinded, randomized split-face trial 25 patients (mean age, 31.9 y) with Fitzpatrick skin types III or IV and moderate-to-severe acne scars	2 treatments given 1 mo apart Entire face treated with fractional CO_2 laser (COFRAX, [AMT, Seoul, Korea]; fluence, 30-70 mJ/cm^2; MTZ,150; spot size, 12 mm; pulse duration in a single pass, 1 ms) followed by (1) Intradermal AA-L-PRP on 1 half of face or (2) Intradermal saline on the other half	- 10 mL of blood was drawn into a syringe prefilled with 1.5 mL of citrate dextrose solution - First spin, 160 $g \times 10$ min - Second spin, 400 $g \times 10$ min - Pellet of platelets was mixed with 1.5 mL of supernatant to make 1.5 mL of PRP - Activator consisting of 1 mL of 3% CaCl was added to make AA-L-PRP - Injections spaced 1- to 1.5-cm intervals (0.02 mL at each site)	Inter-rater agreement by κ statistics showed high congruence between 2 independent raters ($\kappa = 0.7$, $P < .001$) Assessments performed at d 84 as follows: - The mean IGA scores showed that the fractional CO_2 laser plus PRP resulted in an improvement of ~75% vs the 50% seen with a fractional CO_2 laser plus saline ($P < .001$) ECCA scores showed significantly greater improvement with treatment using a CO_2 laser plus PRP ($P < .05$) The mean values reported for a 3-degree visual analogue scale were as follows: - For erythema on the PRP-treated side and control side, 1.2 and 2.2, respectively - For hyperpigmentation on the PRP-treated side and control side, 1.0 and 2.4, respectively - Higher satisfaction scores were reported for the PRP combination therapy ($P = .016$), and scar improvement was greater with PRP combination treatment than in the control on d 7 ($P = .03$) and d 84 ($P = .02$) Skin biopsy specimens (2 mm) for the molecular evaluation were obtained on d 0, d 1, d 3, d 7, and d 28 after the first treatment session; IHC was performed and evaluated with image analysis (Leica QWin, version 3.5.1, Leica Microsystems, Nussloch, Germany): - Higher TGF-β1 ($P = .02$), TGF-β3 ($P = .004$), c-myc ($P = .004$), TIMP ($P = .01$), HGF ($P = .03$), collagen 1, and collagen 3 expression ($P = .03$) in tissue from the PRP treatment group than in the control was noted on d 28 PRP treatment produced increased EGFR expression and decreased keratin 16 in HaCaT cell at 48 h, strongly suggesting that	2b Throughout the study to d 84, epithelization scale scores (total degrees of erythema, swelling, and oozing) were significantly lower for the PRP-treated side ($P < .05$) The degree of erythema was significantly lower on the PRP-treated side than on the saline-treated side throughout the whole study period ($P < .05$)

			PRP may accelerate epithelization and decrease laser-induced skin damage ($P < .05$) Follow-up, 3 mo	
Abdel Aal et al (2018)[43] Single-blinded, comparative, split-face study 30 patients (mean, 24.73 y) with Fitzpatrick skin type III-V and mild-to-severe acne scarring	In 2 treatments at a 3- to 4-wk interval, ablative CO_2 laser (Smartxide DOT; power, 15 W, dwell time, 60μs with 700-μm spacing and smart stack level 3) was applied to both sides of the face followed by: AA-L-PRP on the right side of the face only	- 10 mL of blood was collected in 5 sterile tubes with sodium citrate 3.8% - First spin, 3000 rpm × 7 min - Second spin, 4000 rpm × 5 min - Activator, 0.1 mL of CaCl per 0.9 mL of L-PRP - 2 mL of AA-L-PRP was injected intradermally (0.1 mL at each point 1-1.5 cm apart)	Grading of postacne lesion severity with the qualitative global grading system of Goodman and Barron and global photography evaluated by 2 blinded physicians In clinical improvement, the combination therapy showed significantly better results than the CO_2 laser monotherapy did ($P < .001$) Patients were more satisfied with the combination treatment than with laser monotherapy ($P < .001$) Follow-up, 6 mo after the final treatment	2b At 1 wk after each session, clearance of erythema was faster on the laser plus PRP—treated side ($P = .0052$) PIH occurred on the side treated with a laser alone in 16.6% of patients, whereas no PIH was seen with the combination of laser and PRP treatment
Zhu et al (2013)[44] Prospective, single blinded, cohort study 22 patients (mean age, 28 y) with Fitzpatrick skin type III or IV and moderate-to-severe facial acne scars (6 patients had concomitant acne)	Patients received 3 treatments 1-2 mo apart Full face was treated with an erbium fractional laser (wavelength, 2940 nm; pulse duration, 300-600 μs; pulse energy, 600-1200 mJ [selected according to acne scar level]; microbeam diameter, 2-7 mm; and penetration depth, 18-24 μm) Laser treatment followed by AA-L-PRP applied topically to each area	- 10 mL of blood was collected into a tube containing 1 mL of anticoagulant (not reported) - First spin, 1500 rpm × 10 min - Second spin, 3000 rpm × 20 min - 6-10 mL of PPP and PRP were aspirated, mixed and the L-PRP platelet concentration was 7-10 × 10^5 platelets/μl - Activator, calcium gluconate at a ratio of 1:9	Photography evaluated by 2 blinded dermatologists At 4 wk after the first treatment, the clinical improvement was rated as moderate Physician assessment showed that 90.9% of patients reported excellent or marked improvement after 3 treatments; no patients showed no improvement Patient assessment at 4 wk after treatment completion showed that 91% were satisfied or very satisfied, with 45% wanting to receive further treatment All 6 patients with active acne had resolution Follow-up, 3 mo	4 The mean duration of erythema was 1.86 d; in 77% of cases, erythema lasted <2 d Patients felt burning pain during the procedure that resolved with topical PRP Desquamation was noted for 4-5 d No other adverse events were noted

CaCl, Calcium chloride; *ECCA*, Echelle d'évaluation clinique des cicatrices d'acné; *EGFR*, epidermal growth factor receptor; *HGF*, hepatocyte growth factor; *IGA*, Investigator's Global Assessment; *IHC*, immunohistochemisty; *L-PRP*, leukocyte- and platelet-rich plasma; *MTZ*, microthermal zone; *NA-L-PRP*, Nonactivated, leukocyte- and platelet-rich plasma; *NA-PRP*, non-activated, platelet-rich plasma; *OCT*, optical coherence tomography; *PIH*, postinflamatory hyperpigmentation; *PPP*, platelet-poor plasma; *PRP*, platelet-rich plasma; *TGF-β*, transforming growth factor-β; *TIMP*, tissue inhibitor of metalloproteinase.

whole blood (Table I). Treatment sessions are administered every 2 weeks for a total of 3 to 6 sessions. Although 3 studies have demonstrated that combination therapy with PRP provides improved acne scarring compared with microneedling alone,[32,34,35] others have shown no additive benefits.[33,36,37] Subjectively, patients report higher satisfaction with treatments that utilize PRP, possibly owing to reduced postprocedural erythema and edema. The paucity of studies, small sample sizes, and mixed results represent significant limitations in interpreting the literature; thus, whether the addition of PRP to microneedlng objectively improves acne scarring is unclear. Larger studies with longer follow-up are required to determine the benefits of PRP as an adjunct to microneedling.

With fractional ablative laser treatment, 71.4% of studies (5 of 7) were performed using AA-L-PRP (Table II). Prior reports suggest that the use of elevated leukocyte concentrations in PRP potentially produces negative inflammatory effects mediated through the nuclear factor kappa light-chain enhancer of activated B cells pathway.[45,46] Among the total of 167 patients, the addition of leukocyte- and platelet-rich plasma (L-PRP) to laser ablation produced added benefits in acne scarring in 5 of the 7 studies and improvements in symptoms such as erythema, edema, and pain in 6 of the 7 studies. This argues against concerns regarding leukocytes inducing a detrimental proinflammatory milieu and suggests that L-PRP may expedite wound healing following laser therapy. All studies utilized a 2-spin centrifugation method to produce PRP in 2 or 3 sequential treatment sessions administered 1 month apart, supporting a standardization for this technique. Gawdat et al[40] demonstrated that topical application may be just as effective as intradermal injections of AA-L-PRP when utilized with fractional ablative laser treatment. The microscopic pores created by fractional laser treatment may enhance transepidermal delivery of topical PRP, contributing to its efficacy. Conversely, Kar et al[41] did not show any benefit in scar appearance when using topical nonactivated L-PRP with laser ablation. But both studies documented that adding topical PRP decreased postprocedure side effects, which is attractive, as topical application would avoid painful injections, simplify the therapy, and enhance the overall patient experience. The limitations of the studies reviewed include small sample size and short-term follow-up.

Additionally, variability in laser settings and PRP preparation methods limit comparison between studies. With too little centrifugal force or duration, the platelets may not separate from other cell types. Alternatively, excessive centrifugal forces or duration may produce platelet lysis or push platelets into the buffy coat.[47] In vitro, the highest platelet capture efficiency with preservation of platelet function was noted at 160 *g* for 10 minutes in the first spin and at 250 *g* for 15 minutes in a second spin.[47] An optimal platelet concentration may also exist, as fibroblastic proliferation was greatest with PRP containing 2-fold to 4-fold the peripheral platelet concentration, whereas hyaluronic acid production was greatest with a 2-fold concentration and angiogenesis decreases at concentrations greater than 1.5 million platelets/μL.[48,49]

There is no current standardization in the use of an activator or delivery technique for PRP in the treatment of acne scars. Larger studies are necessary to delineate these parameters and ascertain whether certain patients (ie, those with higher acne scar severity, certain types of acne scars, and different duration of scars) may require more frequent or intensive combination therapies that include PRP.

CONCLUSION

The use of PRP is becoming more prevalent in the field of dermatology. Although the addition of PRP to microneedling offers mixed results, its addition to ablative laser therapy improves acne scarring, patient satisfaction, and postprocedural symptoms.

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