



A Meta-analysis of the Evidence for Assisted Therapy with Platelet-Rich Plasma for Atrophic Acne Scars

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Abstract

Background A number of studies have investigated the role of platelet-rich plasma (PRP) as an assisted therapy for atrophic acne scars. However, the results are diverse, and no up-to-date meta-analysis was found that exclusively examined atrophic acne scar treatment.

Objectives To perform a meta-analysis to assess improvements in the side effects of PRP and the effect of assisted therapy for atrophic acne scars.

Methods This study followed PRISMA guidelines. A comprehensive search of the literature was carried out in September 2018 using the electronic databases of PubMed, EMBASE, MEDLINE, and the Cochrane Library.

Results Seven articles were included in this review. All of the studies published utilized PRP as additive therapy. The major therapies included fractional carbon laser therapy and microneedling. Five studies (249 participants) reported four degrees of improvement on an improvement scale (degrees 3 and 4 were considered improvement in this analysis). Four studies (200 participants) reported mean improvement scores. A significantly higher degree of improvement was shown in the PRP group compared to the control group (OR = 8.19; 95% CI 4.32–15.52; $p < 0.00001$), as well as better mean improvement score (WMD = 23.73; 95% CI 18.60–28.87; $p < 0.00001$).

Substantial heterogeneity was seen in the degree of improvement ($I^2 = 54%$; $p = 0.07$) and the mean improvement score ($I^2 = 75%$; $p = 0.008$). There were overall fewer monitored side effects, including erythema and edema (in days), in the PRP groups; however, no significance was found.

Conclusions This review shows that PRP is a useful assisted therapy for atrophic acne scars, which can achieve better improvement.

Level of Evidence III This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Meta-analysis · Platelet-rich plasma · Atrophic acne scars

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Introduction

A significant majority of adolescents suffer from the problem of acne, and 12–14% of adults experience post-adolescence acne. Acne may commonly leave scarring which leads to subsequent cosmetic and psychological problems [1]. The pathophysiology of acne scar formation was recently proposed to be associated with B cell infiltration, long-term inflammation, and alteration of the structure of sebaceous glands [2].

Research has shown that platelet-rich plasma (PRP) may induce quantifiable amounts of interleukins (ILs), such as IL-1, IL-6, IL-7, and IL-10. In this way, cytokines modulate the inflammatory response [3]. Since PRP was proven to be effective in treating fasciitis, tendinopathy, osteoarthritis, and androgenic alopecia [4–7], some research began to investigate the role of PRP in atrophic acne scar formation. Besides PRP, there are few preexisting treatment strategies for treating acne scars, including laser therapy and mechanical therapy [8]. A number of studies investigated the role of PRP as an assisted therapy for atrophic acne scars. However, the results are controversial, and no up-to-date meta-analyses were found that exclusively examined atrophic acne scar treatment. Thus, we performed a meta-analysis to assess improvements in the side effects and the effect of PRP as assisted therapy for atrophic acne scars.

Methods

The objective of this review was to assess the literature on PRP outcomes for atrophic acne scars. We specifically focused on clinical outcomes in a comparative view, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting this meta-analysis [9].

Search Strategy

Two reviewers (T-S Hsieh and W-K Chiu) independently conducted a systematic review of related articles published up to September 2018 in MEDLINE (via PubMed), the Cochrane Library, and EMBASE. The following keywords were used for the search: “platelet-rich plasma” or “platelet-rich fibrin” or “thrombocyte-rich plasma” in combination with “scars”.

In total, 297 citations were identified. Among these, 18 articles were retrieved for a full review, and seven met the inclusion criteria. A flow diagram is shown according to the PRISMA guidelines.

Study Selection

Article selection was based on an initial screening of titles and abstracts and was followed by a screening of the full texts. The eligibility criteria for studies were: (a) PRP was utilized as a combination tool for treating atrophic acne scars, (b) the efficacy of PRP was assessed in humans, (c) there was complete follow-up (of at least 1 month) and with an objective measure of the improvement (a chromometer, clinical improvement scale, or qualitative scar grading system), and (d) at least eight cases were included.

For the purpose of this analysis, eligible studies were those that reported quantitative outcomes of PRP-assisted therapy compared to control treatment for atrophic acne scars. Each study was independently evaluated by two co-authors (W-K Chiu and T-F Yang) for inclusion or exclusion from this analysis. To be included, studies had to provide details on baseline characteristics, the type of procedure, the method of PRP processing, and outcomes of clinical improvement compared to control patients or normal areas in the same patient (internal control).

Data were independently collected from retrieved articles by two investigators (C Chen and T-S Hsieh) and checked by a third investigator (H-J Wang). Consensus was reached on any disagreements of the collected data. The following data were extracted: first author, year of publication, study design, number of patients, skin types of the patients, mean age of the patients, type of intervention, PRP preparation, injection protocol, mean follow-up time, and primary and secondary measures.

The quality of the included studies was independently assessed by two investigators (T-S Hsieh, and C Chen) using the Quality Assessment Tool for Quantitative Studies.

Outcome Measures

The primary outcome was the improvement scale of four degrees of improvement and the mean improvement score. The lesions were assessed using Goodman’s Qualitative scale and Quantitative scale in pre- and post-treatment evaluation [10, 11]. The Qualitative scale is based on the type of lesion, visibility of lesion, and depth of the scar and categorized into four grades of severity (1–4). The degrees of improvement were also using a quartile grading scale based on the clinical improvement and satisfaction (degree 3 and 4 were considered an improvement in this analysis). The improvement score (Goodman’s Quantitative scale) is a further modification of the above based on the individual lesion count and scores them between 0 and a maximum of 84. Secondary outcomes were the side effects of the therapy, including the durations of erythema and edema.

Statistical Analysis

Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) were utilized for analyzing categorical variables, while the weighted mean difference (WMD) with the 95% CI was used to express differences in continuous variables. Heterogeneity was assessed using the I^2 statistic. We used an inverse variance statistical method and random-effect (or fixed-effect) analysis for the analysis of this meta-analysis [12, 13] because of the observational nature of some studies included in this analysis. A value of $p < 0.05$ was considered statistically significant.

Results

The literature search yielded seven articles pertinent to this issue with sources of information on outcomes using PRP injections for atrophic acne scars (Table 1). The literature search flowchart is shown in Fig. 1.

Comparison of Primary Outcomes Using an Improvement Scale

Five studies reported an improvement scale with four degrees of improvement (degree 3 and 4 were considered an improvement in this analysis). High heterogeneity was observed in this study pool with an I^2 value of 54% (Chi-squared = 8.62), and a fixed-effect model was adopted for this meta-analysis. Significantly better improvement was seen in the PRP group compared to the control group (OR = 8.19; 95% CI 4.32–15.52; $p < 0.00001$) (Fig. 2).

Comparison of the Primary Outcome Using an Improvement Score

Four studies reported a mean improvement score as the primary outcome. High heterogeneity was observed in this study pool with an I^2 value of 75% (Chi-squared = 11.96), and a fixed-effect model was adopted for this meta-analysis. A significantly better mean improvement score was seen in the PRP group compared to the control group; (WMD = 23.73; 95% CI 18.60–28.87; $p < 0.00001$) (Fig. 3).

Comparison of the Side Effect of Edema (in Days)

Three studies were combined to compare the secondary outcome of the side effect of edema (in days). High heterogeneity was observed in this study pool with an I^2 value of 79% (Chi-squared = 9.49), and so a random-effect

model was adopted for this meta-analysis. The side effect of edema showed no significant difference between the PRP group and control group (4.4 days in the PRP group vs. 5.3 days in the control group; WMD = -0.53 ; 95% CI -1.73 to 0.67 ; $p = 0.39$) (Fig. 4).

Comparison of the Side Effect of Erythema (in Days)

Three studies were combined to compare the secondary outcome of the side effect of erythema (in days). High heterogeneity was observed in this study pool with an I^2 value of 57% (Chi-squared = 4.63), and so a random-effect model was adopted for this meta-analysis. The side effect of erythema (in days) showed no significant difference between the two groups, even though there was a better improvement score compared to the control group (4.5 days in the PRP group vs. 6 days in the control group; WMD = -1.07 ; 95% CI -2.39 to 0.25 ; $p = 0.11$) (Fig. 5).

Discussion

Autologous PRP contains the plasma portion of autologously sourced blood with a high iatrogenic platelet concentration [21]. Aside from treating fasciitis, tendinopathy, osteoarthritis, and androgenic alopecia, PRP has also been used in the field of plastic surgery and dermatology for scar remodeling [14, 15, 22–24]. Platelets release growth factors including platelet-derived growth factor and transforming growth factor- β , which facilitate and accelerate bone and soft-tissue regeneration [17, 25–28].

In terms of atrophic acne scars, there are many types of treatments including medical, surgical procedural management, tissue augmentation, and various ablative and non-ablative laser and light energies [29]. Treatment has to be tailored to the patient's needs, tolerance, and goals along with the skin type, and physician's assessment and expectations [20]. In our study, three trials used a fractional carbon dioxide laser as the main treatment, three trials used microneedling, and one trial used subcision (subcutaneous incision-less surgery). Facial resurfacing with the fractional laser is accepted as one of the most effective treatments [30]. An ablative fractional carbon dioxide laser generates heat which can remove dermal tissues and cause tissue shrinkage in the adjacent dermal collagen accompanied by collagen remodeling and skin tightening [31]. Microneedling also has a role as another effective treatment for acne scars. The technique was shown to increase remodeling of the skin by creating thousands of microscopic channels through the epidermis to the dermis. In response to multiple cutaneous injuries and breaking of old collagen strands, a cascade of growth factors (which stimulate the

Table 1 Characteristics of the selected studies

Included studies	Study type/ level of evidence	No. of experiments	No. of Control	Skin type	Mean age/ years	Intervention	PRP preparation	Injection protocol	Mean follow- up	Assessment method
Lee et al. [14]	Simultaneous split-face trial	14 (4 women and 10 men)	14 (normal saline injection)	Type III–V	28.1 (range 21–38)	Combined with ablative carbon dioxide fractional resurfacing	Two-part system (Prosys, T. Cell Bio Inc, Seoul, South Korea) 60 ml of blood transferred to tubes containing anticoagulant at a ratio of 1:10, the mixture was centrifuged at 3000 rpm for 3 min, the separated fraction of PRP and buffy coat was centrifuged at 4000 rpm for 3 min	20 individual sites on the each site of the face (1.5 to 2 cm interval) Each site received 0.3 ml of PRP or normal saline (repeated after 1 month)	30 days (0, 2, 4, 6, 8, 15 and 30)	Erythema: chromometer
Gawdat et al. [15]	Split-face trial	30 (18 female, 12 male)	15	Type III–V	24.8 ± 4.3 (range 19–35)	Combined with fractional carbon dioxide laser	10 ml of blood was mixed with 1.5 ml of anticoagulant solution (acid citrate dextrose) and then centrifuged at 150 xg for 15 min, the fraction with lower red blood cell portion was discarded and centrifuged at 400 xg for 10 min. 1 ml of 3% calcium chloride was added to the 1.5 ml PRP	0.2 ml of autologous PRP injected at 10 different sites at the interval of 1.5 cm	Baseline and 3 months after the last session (6 months after the starting session)	clinical improvement of skin smoothness: Blinded physician viewing digital photograph, four-point scale for Clinical satisfaction of the patient: four-point scale
Asif and Singh [16]	Concurrent split-face trial	50 (Intradermal of PRP and topical PRP)	50 (intradermal injection of distilled water)	Type III–V	25.72 (range 17–32)	Combined with microneedling	Double-spin method, 17 ml of blood mixed with 3 ml of acid-citrate-dextrose anticoagulant, centrifuged at 293.88 g for 5 min, then buffy coat and plasma were further centrifuged at 690.94 g for 17 min, platelet-poor plasma was removed leaving 2 ml PRP	1 ml of the 2 ml PRP was first mixed with 0.1 ml of 10% calcium chloride and injected intradermally, 0.1 ml/cm ² . The other 1 ml was also mixed with 0.1 ml of 10% calcium chloride and allowed to form a platelet gel	Three consecutive session (each at an interval of 1 month) Follow-up for 3 months after the final session	Final independent dermatologist score (poor, fair, good and excellent)

Table 1 continued

Included studies	Study type/level of evidence	No. of experiments	No. of Control	Skin type	Mean age/years	Intervention	PRP preparation	Injection protocol	Mean follow-up	Assessment method
Faghghi et al. [17]	Split-face randomized clinical trial	16	16	Type II–IV	36.8 (range 22–52)	Combined with fractional ablative carbon dioxide	Two-stage centrifuging process, 20 ml mixed with 2.4 ml anticoagulant (citrate phosphate dextrose). The mixture was centrifuged at 2000 g for 3 mins. After discarding the red blood cell portion, the supernatant was centrifuged at 5000 g for 5 min. The resulting platelets were mixed with 4 ml of supernatant with 3% of calcium chloride added as platelet activator	The PRP treated half was selected randomly, injection sites were located at 2 cm intervals with 0.2 ml platelet-rich plasma injected	Baseline, 1 month after the first treatment session, 4 months after the second treatment (1 month after the first)	Clinical improvement: Two blinded dermatologist, Using quartile grading scale Erythema and edema: visual analog scale (0 to 10)
Ibrahim et al. [18]	Comparative, simple randomized, noncontrolled study	34 (18: atrophic acne scar; 10 atrophic post-traumatic scar; 6: post chickenpox)	28 (18: atrophic acne scar; 10 atrophic post-traumatic scar)	Type II–IV	26.33 ± 6.08 (range 16.0 to 40.0)	Combined with microneedling	10–20 ml of blood was mixed with sodium citrate (10:1). The initial centrifugation step is at 1419 g for 7 min, and the resulting plasma supernatant underwent a second centrifugation step at 2522 g for 5 min. The lower 1–2 cc of the plasma was mixed with calcium chloride at ratio of 10:1	0.1 cc of PRP was injected at an interval of 1 cm	3 months after the last session	Clinical assessment: two dermatologist, using quartile grading scale
Deshmukh and Belgaukar [19]	Split-face comparative study	40	40 (Only Subcision)	Type II–V	26.9 (males) 26.7 (females)	Subcision (subcutaneous incision-less surgery)	Double-spin method 20 ml of blood was centrifuged at 800 rpm for 8 min, and the separated plasma and RBCs were centrifuged again at 1200 rpm for 12 min. The lower 1/3rd plasma was resuspended and collected as PRP, and 10% calcium chloride (0.1 ml per 9 ml of PRP) was added	0.1–0.2 ml injected at the base of each scar (1.5 ml to 3 ml in total of each patient)	4 sessions (the interval of each session is 4 weeks) Follow-up: 2 months after the latest session	Goodman and Baron's Qualitative acne scar grading system
El-Domyati et al. [20]	Split face	8	8 (Only dermaroller)	Type III–IV	27.87 ± 2.47 (range 25 to 32)	Combined with microneedling	10 ml of blood was mixed with 2 ml of acid citrate dextrose (ratio of 2:8) and then centrifuged at 252 g for 10 min, plasma centrifuged again at a higher spin 1792 g for 5 min. The calcium gluconate was added to the lower 1/3rd in a ratio of 1:9	Topical application of PRP and left for 5 min	6 sessions of treatment (1 session every 2 weeks for 3 months) Punch biopsies were taken before and after 3 months of treatment	Two blinded dermatologists and 2 independent observers (1–25%, 26–50%, 51–75% and 76–100%)

Fig. 1 Diagram of the study selection process

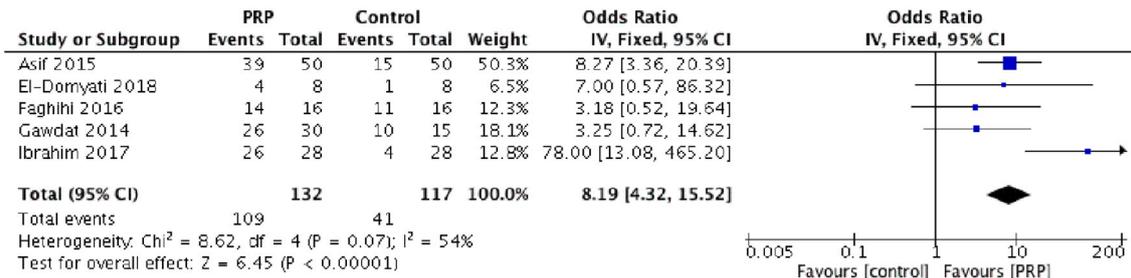
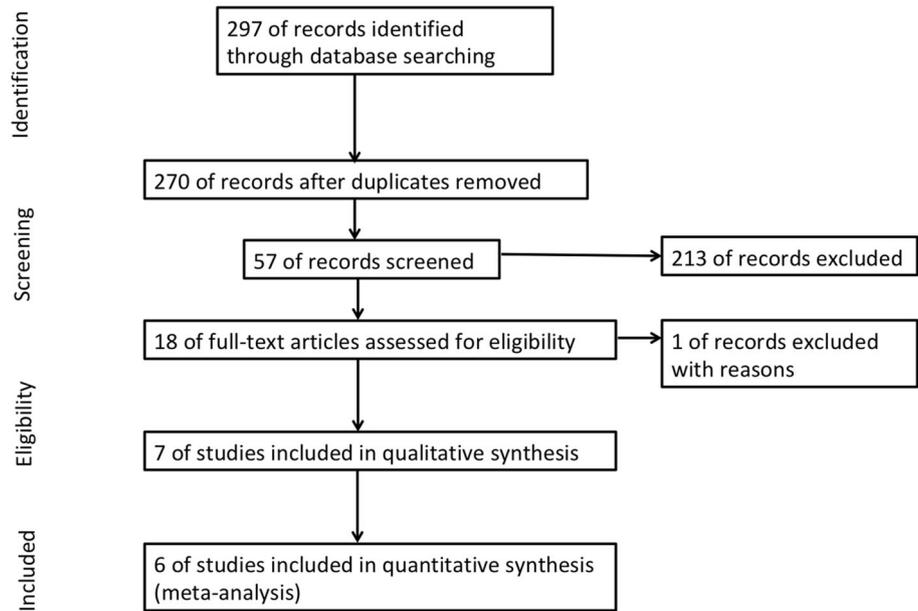


Fig. 2 Forest plot demonstrating the odds ratio of the degree of improvement using an improvement scale in the platelet-rich plasma (PRP) group versus the control group with a fixed-effect model meta-analysis

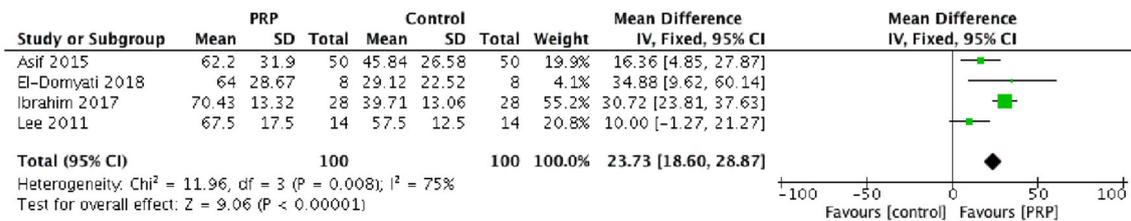


Fig. 3 Forest plot demonstrating the mean difference of the degree of improvement using an improvement score in the platelet-rich plasma (PRP) group versus the control group with fixed-effects model meta-analysis

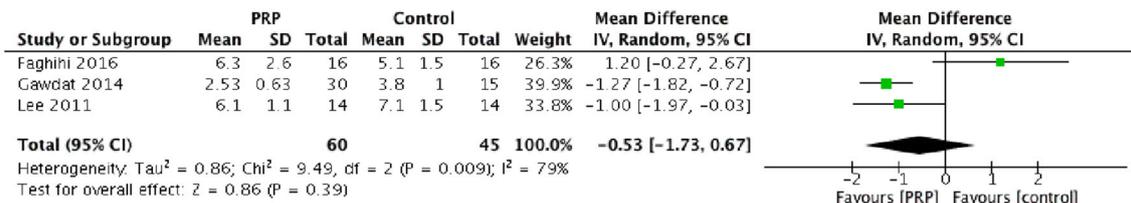


Fig. 4 Forest plot demonstrating the mean difference of the secondary outcome of the side effect of edema in the platelet-rich plasma (PRP) group versus the control group with a random-effect model meta-analysis

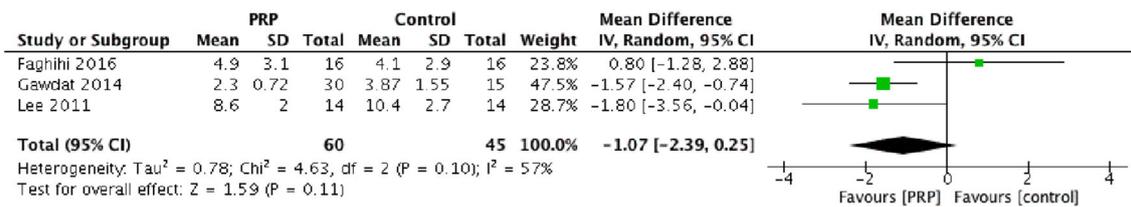


Fig. 5 Forest plot demonstrating the mean difference of the secondary outcome of the side effect of erythema (in days) in platelet-rich plasma (PRP) group versus the control group with a random-effect model meta-analysis

migration and proliferation of fibroblasts) leads to collagen production. Thus, architectural and histopathologic changes take place in the lesional area, and scars are attenuated [32]. Subcision (subcutaneous incision-less surgery) involves therapeutic undermining of depressed scars by cutting the underlying fibrous bands using an 18- to 20-G needle [19]. Only a few studies showed that PRP can be used as adjuvant therapy for atrophic acne [33–36]. However, results are controversial, and no up-to-date meta-analyses were found that exclusively examined atrophic acne scar treatments.

In the current study, the effect of PRP-assisted treatment of atrophic acne scars was assessed. PRP serves as assisted therapy for atrophic acne scars, with the primary therapy including microneedling, a fractional carbon dioxide laser, and subcision. As to the primary outcomes, the degree of improvement and mean improvement score were analyzed with both results yielding significant improvements. These results were compatible with the histochemical findings of an increased epidermal thickness, denser and more-organized collagen fibers, and finer elastic fibers [20]. Another pathway that explains the effect of PRP in the treatment of acne scars could be through the accelerating effect it has on the generation of hyaluronic acid, which is known to draw water into the hyaluronic acid matrix, causing it to swell, which creates volume and skin turgor and lubricates tissues. There are also indications that native hyaluronic acid promotes cell proliferation and extracellular matrix synthesis and modulates the diameter of the collagen fibers, improving atrophic scars [18, 37].

As for side effects, the use of PRP can theoretically enhance the recovery of laser-damaged skin and shorten the duration and degree of postoperative erythema, edema, and crusting. A few clinical studies also showed that patients treated with PRP for acne scars had faster recovery times compared to the control group [14, 35]. The reason is that when tissue is damaged, platelets are the first cells to arrive at the site and play an important role in mediating tissue repair through the release of growth factors from their α -granules [14, 38]. These α -granules contain storage pools of numerous growth factors, including platelet-derived growth factor, transforming growth factor- β , vascular endothelial growth factor, insulin-like growth factor,

fibroblast growth factor, epithelial growth factor, and keratinocyte growth factor, as well as many cytokines, chemokines, and resulting metabolites. Because PRP is, by definition, platelet rich, it contains correspondingly high levels of these autologous growth factors [39]. However, in the current study, the durations of erythema and edema were a few days shorter in the PRP-assisted groups, but the differences did not reach significance in this meta-analysis.

As for PRP preparations, the general preparation method utilizes a two-part system although there were some variations in the preparation of PRP in each study. In addition to differences in interventions and PRP preparations, the injection method also differed, as the interval of injections ranged from 1 to 2 cm and the amount of each injection ranged from 0.1 to 0.3 ml. In addition, in one included study, the application of PRP was topical, and although the effect size of the study was potentially small, there may still have been some discrepancies among the application methods.

As to outcome assessments, two separate blinded dermatologists were most often used to assess the improvement in scar quality with a grading system. A chromometer was applied to assess the side effects. Although the process was blinded, there may still have been some potential judgment bias. The follow-up period ranged from 1 to 3 months. The lasting effect of treatment should be assessed and analyzed in subsequent research to determine the optimal follow-up interval.

The major limitations in this meta-analysis were minimal patient factors and possible confounding factors, as most of the reports preferred to use of a split-face study to systemically study the effect of PRP-assisted therapy. Nevertheless, it limited the number of randomized controlled trials we could find on this topic. The other bias was that we only focus on the effect of assisted therapy with PRP regardless of primary treatment for atrophic acne scar. In our analysis of seven studies, there were only three using CO₂, three using microneedling, and one using subcision as primary treatment. The number was too small to let us control the bias of primary treatment.

Conclusions

This review showed that PRP is a useful assisted therapy for atrophic acne scars, which can achieve better improvement. However, due to a limitation of a small case number, the effects of PRP should be better quantified using a large randomized controlled trial.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Human and Animals Rights Statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

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