

Combining platelet rich plasma with ablative laser for post acne scars: A review

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Abstract

Background: Acne scars are one of the most common sequelae of inflammatory acne. It commonly affects adolescents and young adults and hence is associated with significant psychological morbidity. It is historically resistant to oral as well as surgical modalities. In the last two decades, ablative lasers (fractional or otherwise) have proven to be effective in management of acne scars. Some studies have proven the efficacy of platelet rich plasma in reducing the adverse effects and improving the efficacy of lasers.

Objective: Review of the studies combining platelet rich plasma with ablative laser for post acne scars.

Methods: A literature review of the MEDLINE database for studies evaluating the combination of ablative lasers with platelet rich plasma was performed. Only studies with higher levels of evidence (randomised controlled trials and comparative studies) were included in this review.

Results: Adding intradermal platelet rich plasma to fractional ablative lasers in the management of post acne scars increases clinical efficacy, reduces downtime as well as frequency and duration of ablative lasers related adverse effects. The efficacy of topical platelet rich plasma is less as compared to intradermal platelet rich plasma.

Limitations: The studies analysed are heterogeneous in nature with varied protocols and duration of follow up.

Conclusions: It is recommended to combine the ablative lasers with intradermal platelet rich plasma for better clinical response and reduce adverse effects as well as downtime.

Key words: Ablative lasers, acne scars, combination, fractional lasers, platelet-rich plasma

Introduction

Acne vulgaris is a common dermatosis of pilosebaceous unit affecting up to 80% of adolescents and young adults.¹ Acne scarring as a complication of acne vulgaris is reported to affect up to 14% of them, which may lead to low self-esteem, social withdrawal, psychological depression and reduced quality of life.² Acne scars are classified into three primary types: atrophic, hypertrophic and keloidal. Atrophic scars are by far the most common type which can also be subclassified into ice-pick, rolling and boxcar scars.³ Many acne scar scoring systems have been proposed amongst which

Goodman and Baron's quantitative scoring based on type, number and severity is most commonly used.⁴ They also added a qualitative global grading system, which is a simpler scoring system classifying acne scars as macular, mild, moderate or severe.⁵ Several treatment options are available like chemical peels, chemical reconstruction of skin scars (CROSS) using trichloro acetic acid, dermabrasion, micro-needling, punch floatation, dermal grafting, ablative and non-ablative lasers, intralesional corticosteroids, silicone gels and tissue augmentation using fillers.⁶ Ablative laser resurfacing has been the most effective and has been elevated to the

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status of gold standard.⁷ However, in addition to significant downtime, resurfacing by ablative laser causes additional cutaneous adverse effects such as erythema, edema, post-inflammatory hyperpigmentation, milia, scarring, secondary infections and acneiform eruptions. The introduction of fractional laser therapy has reduced the severity of these adverse effects, but they remain nonetheless.^{8,9} Fractional laser resurfacing relies on producing small zones of micro-damage separated by zones of non-damaged tissue that favour a rapid healing process by promoting formation of new collagen. Platelet-rich plasma is a concentrate of patients' own platelets with growth factors such as platelet-derived growth factor, vascular endothelial growth factor, epidermal growth factor and transforming growth factor beta, which possess immune-modulating properties and promote tissue healing.¹⁰ Thus, platelet-rich plasma has the potential to mitigate the adverse effects caused by lasers in the treatment of acne scarring.^{11,12} Although there are numerous randomised controlled trials (RCTs) and comparative studies proving the efficacy of combining the above two modalities in post acne and other scars, there is only one systematic review and meta-analysis by Chang *et al.*¹³ (2019) and another meta-analysis by Wu *et al.*¹⁴ (2020) that analyzed four and nine studies, respectively. We present a broader review including more studies consisting of higher levels of evidence, that is systematic review, meta-analysis and comparative studies, on combination of the platelet-rich plasma and laser therapy in post-acne scars.

Material and Methods

Search strategy and terms

A literature search was performed for studies combining platelet-rich plasma and ablative lasers (both conventional as well as fractional) in the treatment of acne scars published before 01 Jan 2022. MEDLINE (OVID, from 1948), EMBASE (OVID, from 1980), ahead of print subset fraction from Pubmed- not yet published in OVID MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL) and ongoing trial registries (<http://clinicaltrials.gov/>) were searched without any restrictions in language. A filter was used to identify randomised clinical trials in titles, abstracts, and medical subject headings. Because there were only a few randomised controlled trials, search was broadened to include comparative studies as well. The search was carried out through use of the following keywords: "platelet rich plasma" OR "laser" OR "ablative laser" OR "fractional laser" OR "randomised controlled trial" OR "comparative study."

Inclusion and exclusion criteria

Randomised controlled trials (N > 10) which reported on the efficacy and safety of the combination of platelet-rich plasma with ablative lasers in acne scars were included. Studies where randomization was not done but were split-faced comparative studies were also included. In-vitro, pre-clinical and animal studies, case series, case reports, expert opinions

and studies not fulfilling the inclusion criteria were excluded from the review and analysis.

Selection of studies

Using the keywords mentioned above, the titles and abstracts from electronic literature search were perused and those articles which fulfilled our predefined inclusion criteria were obtained. Thereafter, articles were scanned for exclusion or inclusion. Selecting studies was executed by four reviewers independent of each other (SA, PD, GK and PB). Any disagreements between the three reviewers were resolved by commonly drawn consensus by discussion or intervention by the fifth reviewer (GA).

Data analysis and study quality assessment

Details including the year of publication, authors, type of study, sample size, Fitzpatrick skin type, treatment protocol, statistical analysis, results (primary outcome) and adverse effects (secondary outcome) were reviewed.

Statistical Analysis and Results

Sixteen studies comprising randomised controlled trials as well as split-face comparative studies fulfilled our selection criteria and were included in our review. [Table 1].

The first split-face randomised controlled trial evaluating the combination of fractional CO₂ laser and platelet-rich plasma was conducted by Lee *et al.*¹⁵ in 14 patients. Fractional CO₂ laser was performed a month apart followed by either platelet-rich plasma or normal saline injections on the randomised halves of the face and found significant improvement in physician-assessed quartile grading scale on the platelet-rich plasma side when compared to normal saline side (P = 0.03). There was also a significantly less intensity and duration of erythema on the platelet-rich plasma side than the control side, P = 0.01 and 0.047, respectively. The duration of post-treatment edema and crusting was also significantly less (P = 0.04 each).

Gawdat *et al.*¹⁶ compared the results of three monthly sittings of fractional CO₂ laser followed by intradermal and topical platelet-rich plasma against intradermal normal saline (NS) in 30 patients through a split-face randomised control trial and found significant improvement in physician assessment scale in FCL + PRP groups (topical as well as intradermal) as compared to intradermal normal saline group (P = 0.03). There was no significant difference in the grades of clinical improvement between intradermal and topical platelet-rich plasma. There was significantly shorter duration of erythema, edema, crusting, post-inflammatory hyperpigmentation (PIH) and acneiform eruption in FCL + PRP groups (P = 0.02) and the total downtime was shorter in FCL + PRP groups (P = 0.02). Pain was significantly greater in FCL + intra dermal PRP groups (P = 0.005) as compared to topical platelet-rich plasma with fractional CO₂ laser.

Faghihi *et al.*¹⁷ in a two-session, randomised split-face study on 16 participants found higher overall clinical improvement

Table 1: Randomised controlled trials and comparative split face studies which met the inclusion criteria and selected in this study (n = 16)

| Author and year of publication | Study design | No of participants | Baseline disease severity | Treatment protocol | Study period and follow up | Evaluation of outcome | Results | Adverse effects |
|------------------------------------|-----------------------------|--------------------|---|---|--|---|--|---|
| Lee et al ¹⁵ , 2011 | randomised split face study | 14 | Moderate to severe acne scars with Fitzpatrick skin types III-V | Fractional CO ₂ laser a month apart followed by either PRP or normal saline injections on the randomised halves of the face | 02 sessions each a month apart; follow up of 04 months after the last session. | Physician assessed improvement in quartile grading scale, adverse effects (edema and erythema) on grading scale on the PRP side (p = 0.03) | Significant improvement in physician assessed quartile grading scale on the PRP side (p = 0.03) | Significantly less intensity and duration of erythema on the PRP side than on the control side. (p = 0.01 and 0.047) respectively. Significantly less duration of post treatment edema and crusting (p = 0.04 each) |
| Gawdat et al ¹⁶ , 2014 | randomised split face study | 30 | Atrophic acne scars with Fitzpatrick skin types III-V | Fractional CO ₂ laser a month apart followed by either intra dermal PRP or topical PRP or intra dermal normal saline injections on the randomised halves of the face | 03 sessions each a month apart; final assessment 03 months after the last session. | Physician assessed improvement in quartile grading scale, clinical satisfaction of patients on a four point scale, depth of acne scars using optical coherence tomography (OCT) | Significant improvement in FCL+PRP groups (topical and intra dermal) as compared to intra dermal normal saline group (p = 0.03) on the physician assessment scale. No significant difference in grades of clinical improvement between intra dermal and topical PRP. | Significantly shorter duration of erythema, edema, mild crusting, PHH, and acneiform eruption (P = 0.02) in FCL+PRP groups. Significantly shorter total downtime (P = 0.02) in FCL+PRP groups. Pain was significantly greater in FCL+ intra dermal PRP groups as compared to topical PRP and with FCL alone. (P = 0.005) |
| Faghihi et al ¹⁷ , 2015 | randomised split face study | 16 | Fitzpatrick skin types II-IV with moderate to severe atrophic acne scars (predominantly rolling and boxcar types with fewer than 20% of the icepick type) | Fractional CO ₂ laser a month apart followed by either intra dermal PRP or intra dermal normal saline injections on the randomised halves of the face | 02 sessions each a month apart; assessed at 01 month after the first session and 04 months after the second. | Physician assessed improvement in quartile grading scale, clinical satisfaction of patients on a four point scale, participant assessed visual analog scale (0 to 10) for erythema and edema on days 0, 2, 4, 6, 8, 15 and 30 after each treatment session. | Overall clinical improvement on physician assessed quartile grading scale of acne scars was higher on the FCL+PRP side but the difference was not statistically significant either 1 month after the first session (P = 0.15) or 4 months after the second (P = 0.23). The patient assessed four point clinical satisfaction scale too showed similar greater clinical improvement but not significant at either 01 or 04 months. (P = 0.18 and P = 0.12 respectively) | Significantly more erythema on FCL+PRP side than control side with on days 0, 2 and 4. (P = 0.003, P = 0.007, P = 0.03 respectively) Also more edema on FCL+PRP side compared with the control side with a statistically significant difference on the days 0, 2 and 8 (P = 0.003, P = 0.004, P = 0.004 respectively). Mean duration of both erythema and edema were greater on the FCL+PRP side but not statistically significant. |
| Shah et al ¹⁸ , 2017 | randomised split face study | 30 | Moderate to severe atrophic acne scars (Grade II-IV) | Fractional CO ₂ laser a month apart followed by either PRP or normal saline injections on the randomised halves of the face | 04 sessions each a month apart; monthly follow up of 04 months after the last session. | Goodman and Baron quantitative global acne scarring grading system, physician assessed improvement in quartile grading scale, patient satisfaction based on scar severity. | Significant reduction in Goodman and Baron grading in both PRP injection site (mean was 14.83 at baseline and 4.2 at four months) and normal saline injection site (mean Goodman and Baron grading was 15.23 at baseline and 7.5 at four months) | Significantly lower proportion of patients in the PRP group had persistent erythema, edema and pain as compared to the normal saline group. (p value = 0.0453, 0.008829 and 0.0076 respectively. |

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|--|------------------------------|----|--|--|---|--|--|--|
| Kar <i>et al</i> ¹⁹ , 2017 | Comparative split face study | 30 | Fitzpatrick skin types III-V with moderate to severe atrophic acne scars | Fractional CO ₂ laser at monthly intervals followed by topical PRP on left side and no intervention on the right side of the face | 03 sessions every month; assessed a month after third session. | Quantitative global acne scar grading system of Goodman and Baron, visual scar assessment questionnaire was also filled up by the observer and patient, patient satisfaction score on a scale of 0–10, procedure-related adverse events (i.e. erythema, edema, and pain) on a visual analog scale of 0–10. | Though there was significant improvement on both sides of the face, there was no significant difference in the quality of scars between the right and the left sides of the face ($P = 0.289$). The addition of topical PRP to FCL on the left side of the face did not result in superior scar improvement as compared to the right side. | The redness, swelling, and pain experienced by each patient were significantly lesser on the side treated with FCL + PRP (left side) than that on the FCL-only side ($P < 0.05$) |
| Min <i>et al</i> ²⁰ , 2017 | randomised split face study | 25 | Fitzpatrick skin types III-V with moderate to severe acne scars | Fractional CO ₂ laser a month apart followed by either intra dermal PRP or intra dermal normal saline injections on the randomised halves of the face | 02 sessions, four weeks apart. Subjects were followed-up on days 1, 3, 7 and 28 after each session and at 1 and 2 months after the final session. | 5-point Investigator's Global Assessment (IGA) for efficacy, Echelle d' evaluation Clinique des Cicatrices d' Acne (ECCA) scores, and a subtype (ice pick, boxcar, rolling scar) analysis, degree of erythema analysis. Skin biopsy specimens (2mm) for the molecular analysis on days 0, 1, 3, 7, and 28 after the first treatment session. | The mean IGA score on the FCL+PRP side was significantly greater than FCL+NS ($P<0.001$). Skin recovery rates after treatment as assessed using the epithelization scale showed significant difference between the two modalities on day 1 ($P = 0.01$). Patients reported significantly higher scores for improvement on FCL+PRP side as compared to NS+PRP side on days 7 ($P=0.03$) and 84($P=0.02$). IHC showed significantly increased expression of TGFβ1, TGFβ3, c-myc, TIMP, HGF, collagen-1 and collagen-3 on FCL+PRP side. | Both the erythema index and colorimetric measurements revealed consistently less erythema of the PRP-treated side compared with the control side. The mean values of 3-degree visual analogue scale (VAS) for erythema on the PRP-treated side and control side were 1.2 and 2.2 respectively. |
| Abdel-Maguid <i>et al</i> ²¹ , 2017 | randomised split face study | 33 | Fitzpatrick skin types III-IV with moderate to severe atrophic acne scars (rolling, boxcar scar and ice pick scar) | Group I- FCL a month apart followed by either topical stem cell cultured medium (SC-CM) or topical normal saline (NS) on randomised halves of the face. Group II- FCL a month apart followed by either topical PRP or topical normal saline (NS) on randomised halves of the face. | 03 sessions each a month apart; assessed monthly and final assessment 03 months after the last session. | Echelle d' evaluation Clinique des Cicatrices d' Acne (ECCA) scores, physician assessed improvement in quartile grading scale, clinical satisfaction of patients on a four point scale, intensity as well as erythema and edema on patient assessed scale; dermatologist assessed PIH, secondary infection, acne activation, bleeding, erosion, and scarring. Histopathological examination for collagen fibres quantitative pro-collagen I gene expression analysis using RT-PCR. | In group I, difference in two sides showed no statistically significant results in any of the three scar types, group II showed greater reduction on the sides treated with FCL+PRP compared to the FCL+SC-CM sides ($P= 0.006$). Marked increase in organized collagen deposition were noted in FCL+PRP and FCL+SC-CM compared to FCL alone. Both FCL+PRP treated sides and the FCL+SC-CM sides had more up-regulation of type I pro-collagen compared to the sides treated by FCL only ($P= 0.001$ and $P= 0.041$ respectively). | There was no significant difference in the duration of erythema, edema, crusting or post-inflammatory hyperpigmentation between the two sides in either group ($P > 0.05$). |

(Continued)

Table 1: (Continued)

| Author and year of publication | Study design | No of participants | Baseline disease severity | Treatment protocol | Study period and follow up | Evaluation of outcome | Results | Adverse effects |
|--------------------------------------|----------------------------------|--------------------|--|--|---|---|---|---|
| Abdel Aal et al ²³ , 2018 | Comparative split face study | 30 | Fitzpatrick skin types III-V with atrophic acne scars | Fractional CO ₂ laser three to four weeks apart followed by either intra dermal PRP on right side and no intervention on the left side of the face | 02 sessions each three to four weeks apart; assessed at six month after the second session. | Qualitative global acne scar grading system of Goodman and Baron, Physician assessed quartile grading scale of Ianzi and Alster, patient assessed subjective questionnaire for satisfaction, Clinician Erythema Assessment Scale, patient assessed questionnaire for presence or absence of adverse effects | The overall improvement of the right side (FCL+PRP) was better than the left side (control) with a statistically significant difference (P<0.0001) | Clearance of erythema was significantly faster on the right side (FCL+PRP) than the left side (control) (P=0.0052). There was no PIH on right side in any of the patients, while it was seen on the left side in five patients (16.6%). Acneiform eruption were significantly reduced on the FCL+PRP side as compared to control. Patients were satisfied with outcome on their right side more than their left with a statistically significant difference (P<0.001) |
| Taweel et al ²³ , 2018 | Comparative non-split face study | 40 | Fitzpatrick skin types II-IV with atrophic acne scars (rolling, boxcar scar and ice pick scar) | Patients were divided into two groups: Group A- three sessions of FCL+ intra-dermal PRP each a month apart. Group B- three sessions of intra-dermal PRP followed by intra-dermal CO ₂ gas injections into scars. (carboxytherapy) | Patients were assessed after a week of each session for complications (edema, PIH and pain) and then for 3 months after the last session. | Physician assessed improvement in quartile grading scale showed significant improvement of acne scars in group A compared to group B (P= 0.039) with no statistically significant differences between the two groups in patients' satisfaction. | Physician assessed improvement in quartile grading scale showed significant improvement of acne scars in group A compared to group B (P= 0.039) with no statistically significant differences between the two groups in terms of pain and PIH. | |
| Galal et al ²⁴ , 2019 | randomised split face study | 21 | Atrophic acne scars | Fractional CO ₂ laser at monthly intervals followed by topical PRP on left side and no intervention on the randomised halves of the face. | 03 sessions each a month apart; assessed monthly at every session followed by every 03 months for a year | Quantitative global acne scar grading system of Goodman and Baron, Antera scoring system of scar depth, patient satisfaction score for scar, pigmentation and redness. | The quantitative global acne scar grading system of Goodman and Baron showed a statistically significant reduction for both sides of the face (P<0.0001) after treatment. Greater reduction was found on the FCL+PRP side. Significant improvement in redness and pigmentation was seen on FCL+PRP side (P < 0.0001). According to the Antera scoring system, 70% of patients on the FCL+PRP side showed good or excellent improvement as compared to only 30% of patients on the FCL side. | Patient satisfaction score on reduction of pigmentation and redness was higher for the sides that were treated with FCL+PRP. |

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|---|--|----|--|--|--|---|--|---|
| El-Taieb <i>et al</i> ²⁵ , 2019 | randomised Clinical Trial (Non split faced) | 75 | Fitzpatrick skin types III-IV with atrophic acne scars (rolling, boxcar scar and ice pick scar) | Enrolled patients were randomly assigned into three groups of every 04 weeks, 25 each. Group A- 12 sessions of intra-dermal injection of PRP at 2-week intervals. Group B- six sessions of fractional Er-YAG laser at 4-week intervals. Group C- combination of the two treatment modalities. | Study period 24 weeks, assessed final assessment at 24 weeks. | Qualitative scarring grading system of Goodman and Baron, physician assessed improvement in quartile grading scale, clinical satisfaction of patients on a four point scale, degree of facial erythema was evaluated by clinician erythema assessment (CEA) scale | Patients treated with Er-YAG laser+ PRP showed significant improvement compared with those treated with Er-YAG laser or PRP alone (P = 0.007 and P=0.001, respectively). Also, patients treated with Er-YAG laser showed significantly greater improvement than those treated with PRP (P=0.001). Patients in group C were more satisfied with their results than those in group A or B (P=0.001 and P = 0.005, respectively). Likewise, patients treated with Er-YAG laser were markedly more satisfied than those treated with PRP alone (P = 0.009). | No statistically significant differences between the study groups regarding any of the post treatment complications in form of erythema, PIH or acneiform eruptions. |
| Arsiwala <i>et al</i> ²⁶ , 2020 | randomised Clinical Trial (Non split faced) | 25 | Fitzpatrick skin types III- V with atrophic acne scars (rolling, boxcar scar and ice pick scar) | Patients were randomly divided into two groups: Group A- treated for three monthly sessions of FCL+ topical PRP and Group B- FCL monotherapy. | Three monthly treatment sessions for 12 weeks; follow up at every monthly visit with final assessment at 12 weeks. | Goodman and Baron quantitative global acne scar grading system, patient assessment of improvement of acne scars on a visual analog scale (VAS). | The mean change in Goodman and Baron quantitative global acne scar grading system scores reduced significantly both in Group A and B (both P < 0.0001) but when compared head to head the difference was statistically insignificant (P = 0.129) | Immediate adverse effects (erythema, edema, and pain) were more in group B but the difference was not statistically significant. Long-term adverse effects (PIH, pain, erythema, acne and secondary infection) too were observed in increased frequency subjects in Group B even though no significant difference was observed between two groups. |
| Mahamoud <i>et al</i> ²⁷ , 2020 | randomised split face study | 30 | Fitzpatrick skin types III-V with mild to severe atrophic acne scars | Fractional CO ₂ laser 04 weeks apart followed by either intradermal hyaluronic acid (HA) injections or PRP injections on randomised halves of the face. | Three treatment sessions, final assessment at three months after the last session. | Qualitative scarring grading system of Goodman and Baron, quantitative global acne scar grading system of Goodman and Baron, clinical satisfaction of patients on a four point scale, subjective evaluation by patients adverse effects like downtime, persistent erythema, edema, PIH, pain, scarring, milia and infections; scoring for pain by universal pain screening with a 0-10 pain intensity numeric rating scale (NRS) | Both FCL+PRP and FCL+HA side achieved statistically significant difference by Goodman and Baron quantitative as well as qualitative scores (P < 0.001). Pitched against one another, the qualitative score showed no statistically significant difference (P = 0.921) denoting that both modalities of treatment gave similar net results. | There was no significant difference between both sides in terms of adverse effects. |

(Continued)

Table 1: (Continued)

| Author and year of publication | Study design | No of participants | Baseline disease severity | Treatment protocol | Study period and follow up | Evaluation of outcome | Results | Adverse effects |
|---|---------------------------------|--------------------|---|---|--|---|---|---|
| Sujana <i>et al</i> ²⁸ , 2020 | randomised non-split face study | 80 | Mild, moderate and severe acne scars | Eighty patients were randomly assigned into two groups of 40 each. Group A was treated with FCL alone, while Group B was treated with FCL + intradermal PRP for 6 months. | A total of six sittings performed at 04 week intervals. Final assessment was done at 04 weeks after the final session. | Goodman and Baron's global acne scarring system, physician assessed improvement in quartile grading scale, subjective assessment was done by patients themselves on a 5-point visual analog scale; duration of erythema, edema and crusting. | In Goodman and Baron's global acne scarring system, patients treated with FCL+PRP responded better to treatment than those treated with FCL alone. Photographic assessment revealed improvement of skin texture and decreased downtime in FCL+PRP group. Patients' subjective assessment too was consistent with results of Goodman and Baron's objective scoring system. | Duration of erythema, edema and crusting was less in FCL+PRP group. Less number of patients experienced PIH in FCL+PRP group too. However more patients experienced pain in the FCL+PRP group. |
| El-Hawary <i>et al</i> ²⁹ , 2021 | randomised non-split face study | 60 | Fitzpatrick skin types III-IV with moderate to severe atrophic acne scars | Sixty patients were randomly divided into three groups. Group 1- intra-dermal PRP injections only, group 2- FCL only, group 3- FCL+ intra-dermal PRP injections. | Each group received three sessions at monthly intervals. Final assessment at 3 months after the last session. | Qualitative scarring grading system of Goodman and Baron, physician assessed improvement in quartile grading scale, clinical satisfaction of patients on a four point scale, patient reported side effects on a 5-point scale, skin biopsies were obtained before and 1 month after treatment sessions. | Significantly higher improvement in group 2 compared to group 1 (P = 0.028) and significantly higher improvement in group 3 than in group 1 (P = 0.002). However, no significant difference was between group 2 and group 3 (P = 0.657). Similar results in satisfaction of patients scale in skin texture, scar appearance and overall satisfaction. Significant increase in epidermal thickness, percentage of collagen fibers, and the number of proliferating epidermal cells (Ki-67 expression) in all three groups before and 1 month after the last treatment session. | Pain was more severe in group 3 while erythema, edema, and crust formation were more severe and of longer duration in group 2. The total downtime was shorter in group 3 (4.60 ± 0.84) than in group 2 (5.40 ± 1.07). |
| Sharma <i>et al</i> ³⁰ , 2021 | Split face comparative study | 30 | Moderate to severe acne scars | Right half- FCL+PRP injections, left half FCL+NS injections | Four treatment sessions four weeks apart. Final assessment was performed two months after the last session. | Goodman and Baron's qualitative acne scar grading system scale, Patient's subjective score. | Improvement in Goodman and Baron's qualitative acne scar grading system scale on both sides was statistically significant (P = 0.000). | Most common side effects reported were erythema and burning followed by edema, which was seen in 63.3% patients on the study side and in 90% patients on the control side. |

PRP: Platelet Rich Plasma; PIH: Post Inflammatory Hyperpigmentation; SC-CM: Stem Cell-Conditioned Medium; FCL: Fractional CO2 Laser; IGA: Investigator's Global Assessment; IHC: Immuno-Histo-Chemistry; Abbreviations: FCL: Fractional carbon dioxide laser; PRP: Platelet rich plasma; NS: Normal saline; OCT: Optical coherence tomography; PIH- Post inflammatory hyperpigmentation; ECCA: Echelle d' evaluation Clinique des Cicatrices d' Acne; PCR: Polymerase chain reaction; IHC: Immuno-histochemistry; TGFβ1: Transforming growth factor beta 1; TGFβ3: Transforming growth factor beta 3; e-myc- cellular mycelytomatosis; TIMP: Tissue inhibitors of metalloproteinases; HGF: Hepatocyte growth factor; SC-CM: stem cell cultured medium; RT-PCR: Reverse transcriptase polymerase chain reaction; CEA: Clinician erythema assessment; HA: hyaluronic acid.

on FCL + PRP side when compared to FCL + NS side, but the difference was not statistically significant by physician-assessed quartile grading scale either 1 month after the first session ($P = 0.15$) or 4 months after the second ($P = 0.23$). The patient-assessed 4-point clinical satisfaction scale also showed similar greater but insignificant clinical improvement on FCL + PRP side at 1 or 4 months ($P = 0.18$ and $P = 0.12$, respectively). However, significant erythema was seen on FCL + PRP side than the control side on Days 0, 2 and 4 ($P = 0.003$, $P = 0.007$ and $P = 0.03$, respectively). Likewise, significant edema was seen on the FCL + PRP side as compared to control on Days 0, 2 and 8 ($P = 0.003$, $P = 0.004$ and $P = 0.004$, respectively). Similar to intensity, the mean duration of both erythema and edema were greater on the FCL + PRP side but was not statistically significant.

Shah *et al.*¹⁸ in 2017 performed a randomised split-face study on 30 patients who underwent four monthly sessions of fractional CO₂ laser followed by either platelet-rich plasma or normal saline injections on the two halves of the face and concluded that there was a significant reduction in Goodman and Baron grading in both platelet-rich plasma (mean was 14.83 at baseline and 4.2 at 4 months) and normal saline injection sites (mean Goodman and Baron grading was 15.23 at baseline and 7.5 at 4 months). Fourteen treatment sites (23.3%) showed excellent response to treatment, out of which 10 belonged to platelet-rich plasma sites and four belonged to normal saline site. Good improvement was seen in 19 treatment sites (31.7%) of which 12 were treated with platelet-rich plasma and seven were treated with normal saline. Significantly higher proportion of patients in the normal saline group had persistent erythema, edema and pain as compared to the platelet-rich plasma group ($P = 0.0453$, 0.008829 and 0.0076, respectively).

Kar *et al.*¹⁹ in a comparative split-face study performed fractional CO₂ laser at monthly intervals followed by application of topical platelet-rich plasma, and no intervention on left and right sides of their faces, respectively, in 30 patients inferred that although significant improvement was seen on both sides of the face as compared to the baseline, there was no significant difference in improvement between the right and the left sides of the face ($P = 0.2891$). However, adverse effects such as redness, swelling and pain experienced by each patient were significantly lesser on the side treated with FCL + PRP (left side) than that on the FCL-only side ($P < 0.05$).

Min *et al.*²⁰ through a randomised split face study studied platelet-rich plasma-induced collagen production and modulation of laser-induced inflammation after fractional CO₂ laser sessions correlating with increased clinical efficacy in acne scars. They used fractional CO₂ laser a month apart, followed by either intradermal platelet-rich plasma or intradermal normal saline injections on the randomised halves of the face. Skin biopsy specimens for molecular analysis were sent on days 0, 1, 3, 7 and 28

after the first treatment session. They found that the mean 5-point investigator's global assessment (IGA) score on FCL + PRP side was significantly greater than FCL + NS ($P < 0.001$). Skin recovery rates after treatment as assessed using epithelization scale showed a significant difference between the two treatment modalities on day 1 ($P = 0.01$). Patients reported significantly higher scores for improvement on FCL + PRP side as compared to NS + PRP side on days 7 ($P = 0.03$) and 84 ($P = 0.02$). Immunohistochemistry showed significantly increased expression of TGFβ1, TGFβ3, c-myc, TIMP, HGF, collagen-1 and collagen-3 on FCL + PRP side. Both erythema index and colorimetric measurements revealed consistently less erythema of the platelet-rich plasma-treated side compared to the control side.

Abdel-Maguid *et al.*²¹ through a split-face randomised study evaluated the efficacy of stem cell-conditioned medium (SC-CM) versus platelet-rich plasma as an adjuvant to fractional CO₂ laser resurfacing for acne scars in 33 patients. After each fractional CO₂ laser session, group I received either topical stem cell-conditioned medium or topical normal saline (NS) on randomised halves of the face, whereas group II- received either topical platelet-rich plasma or topical normal saline (NS) on the randomised halves. In group I, difference in two sides showed no statistically significant results; on the other hand, group II showed greater reduction on the sides treated with FCL + PRP compared to the FCL + SC-CM sides ($P = 0.006$). In blinded physician assessment, the difference between FCL + SC-CM and FCL-only treated sides was insignificant in group I ($P = 0.245$). While in group II, there was significantly better improvement on the FCL + PRP side, which showed excellent marked improvement in 83% of patients, compared to 39% of patients on the FCL + SC-CM side ($P = 0.033$). Marked increase in organised collagen deposition was noted in FCL + PRP and FCL + SC-CM compared to fractional CO₂ laser alone. Both FCL + PRP treated sides and the FCL+SC-CM sides had more up-regulation of type I pro-collagen compared to the sides treated by fractional CO₂ laser only ($P = 0.001$ and $P = 0.041$, respectively). There was no significant difference in the duration of erythema, edema, crusting or post-inflammatory hyperpigmentation between the two sides in either group ($P > 0.05$).

Abdel Aal *et al.*²² in a comparative split-face study in 30 patients using fractional CO₂ laser followed by intra dermal platelet-rich plasma and no intervention on right and left sides of the face, respectively, for two sessions found that the overall improvement of the FCL + PRP side was better than the control with a statistically significant difference ($P < 0.001$). Clearance of erythema was significantly faster on FCL + PRP side than that of the control ($P = 0.0052$). There was no post-inflammatory hyperpigmentation (PIH) on FCL + PRP side in any of the patients, while it was seen in five patients on the control side (16.6%). Acneiform eruptions too were significantly reduced on the FCL + PRP side as compared to the control. Patients were satisfied with the outcome on their

FCL + PRP side more than their control with a statistically significant difference ($P < 0.001$).

Taweel *et al.*²³ in 2018 performed a comparative non-split-face study in 40 patients who were divided into two groups: group A received three sessions of FCL + intradermal platelet-rich plasma each a month apart; group B received three sessions of intradermal platelet-rich plasma followed by intradermal carbon dioxide (CO₂) gas injections into the scars with a flow rate at 80 cc/min using 30G needle (carboxy therapy). Physician-assessed quartile grading scale showed significant improvement of acne scars in group A compared to group B ($P = 0.039$); with no statistically significant differences between the two groups in patients' satisfaction. A significant increase in the incidence of edema was present in 90% of group A patients, while it was seen in only 50% of the patients in group B. There was no statistically significant difference between the two groups in terms of pain and post-inflammatory hyperpigmentation.

In line with studies with similar protocol by Kar *et al.*¹⁹ and Abdel Aal *et al.*,²² Galal *et al.*²⁴ performed a randomised split-face study on 21 patients who received fractional CO₂ laser at monthly intervals followed by topical fractional CO₂ laser and no intervention on the randomised halves of the face. The quantitative global acne scar grading system showed a statistically significant reduction for both sides of the face ($P < 0.0001$); however, greater reduction was found on the sides of the face that was treated with combined laser and PRP. FCL + PRP side showed significantly greater improvement in redness and pigmentation too ($P < 0.0001$). On assessment by Antera scoring system of scar depth, 70% of patients on the FCL + PRP side showed good or excellent improvement as compared to 30% of patients on the fractional CO₂ laser-only side. Improvement in scar appearance and skin texture, as well as decreased pores and pigmentation, were reported by the patients. Patient satisfaction score on reduction of scar, pigmentation and redness was higher for the sides that were treated with combined laser and platelet-rich plasma.

A non-split-faced study by El-Taieb *et al.*²⁵ was the only randomised control trial combining fractional erbium-yag (Frac Er:Yag) laser and platelet-rich plasma. Totally, 75 subjects were enrolled into three groups of 25 each. Group A received 12 sessions of intradermal injection of platelet-rich plasma at 2-week intervals; group B received six sessions of fractional Frac Er:Yag laser at 4-weeks interval; and group C received a combination of the two treatment modalities. Patients treated with Frac Er:Yag laser + PRP showed significant improvement compared with those treated with Frac Er:Yag laser or platelet-rich plasma alone ($P = 0.007$ and $P = 0.001$, respectively). Also, patients treated with Frac Er:Yag laser showed significantly greater improvement than those treated with platelet-rich plasma ($P = 0.001$). According to the clinical satisfaction of patients on a 4-point scale, patients in group C were more satisfied with their results than those in group A or B ($P = 0.001$ and $P = 0.005$,

respectively). Likewise, patients treated with Frac Er:Yag laser were markedly more satisfied than those treated with platelet-rich plasma ($P = 0.009$). There was no statistically significant difference between the study groups regarding any of the post-treatment erythema, post-inflammatory hyperpigmentation or acneiform eruptions.

Similar to the protocol followed by Abdel Aal *et al.*,²² Kar *et al.*¹⁹ and Galal *et al.*²⁴; Arsiwala *et al.*²⁶ in a non-split-faced randomised clinical trial in 25 patients compared three monthly sessions of fractional CO₂ laser + topical platelet-rich plasma (group A) with fractional CO₂ laser monotherapy (group B). Although the mean change in Goodman and Baron quantitative global acne scar grading system scores reduced significantly in both groups A and B ($P < 0.0001$), the head-to-head comparison was statistically insignificant ($P = 0.129$). Both immediate as well as long-term adverse effects were more in group B, but the difference from group A was statistically insignificant.

Mahamoud *et al.*²⁷ (2020) performed a randomised split-face study consisting of 30 subjects who received fractional CO₂ laser sessions 4-weeks apart followed by either intradermal hyaluronic acid (HA) injections or platelet-rich plasma injections on randomised halves of the face. Both FCL + PRP and FCL + HA sides achieved statistically significant differences by Goodman and Baron quantitative as well as qualitative scores ($P < 0.001$). When compared against one another, the qualitative score showed no statistically significant difference ($P = 0.921$).

Sujana *et al.*²⁸ in a randomised non-split-face study in 80 subjects evaluated the efficacy and safety of fractional CO₂ laser alone and in combination with intradermal platelet-rich plasma. Group A was treated with fractional CO₂ laser alone, while Group B was treated with FCL + PRP for 6 months. By Goodman and Baron's global acne scarring scoring system, patients treated with FCL + PRP responded better to treatment than those treated with fractional CO₂ laser alone. Photographic assessment revealed improvement of skin texture and decreased downtime in FCL + PRP group. Patient's subjective assessment was also consistent with the results of Goodman and Baron's objective scoring system. Duration of erythema, edema and crusting was less in FCL + PRP group. Smaller number of patients experienced post-inflammatory hyperpigmentation in the FCL + PRP group too. However, more patients experienced pain in the FCL + PRP group.

El-Hawary *et al.*²⁹ conducted a randomised non-split-face study in 60 patients in which they were divided into three groups: Group 1 – platelet-rich plasma injections only, Group 2 – fractional CO₂ laser only, and Group 3 – FCL + intradermal platelet-rich plasma injections. They reported significantly higher improvement in group 2 compared to group 1 ($P = 0.028$) and significantly higher improvement in group 3 than in group 1 ($P = 0.002$). However, no significant difference was noted between groups 2 and 3 ($P = 0.657$).

There was a similar pattern of outcomes in patient-assessed scale in skin texture, scar appearance and overall satisfaction. There was a significant increase in epidermal thickness, percentage of collagen fibres and number of proliferating epidermal cells (Ki-67 expression) in all three groups before and 1 month after the last treatment session. Pain was more severe in group 3, while erythema, edema and crust formation were more severe and of longer duration in group 2. The total downtime was shorter in group 3 (4.60 ± 0.84) than in group 2 (5.40 ± 1.07).

Sharma *et al.*³⁰ (2021) in a split-face study, comprising 30 patients, compared right half (FCL + PRP injections) with left (FCL + NS injections) over four treatment sessions 4-weeks apart. Significant improvement in Goodman and Baron's qualitative acne scar grading system scale on both sides were reported ($P = 0.000$). Most common side effects reported were erythema and burning followed by edema, which was seen in 63.3% patients on the study side and in 90% patients on the control side.

Discussion

The randomised control trials included in this review combined FCL/Frac Er:Yag and platelet-rich plasma and most of them compared it with normal saline as control. The method of delivery of platelet-rich plasma was broadly of two types, intradermal injection or topical application. The efficacy of FCL/Frac Er:Yag + PRP injections when compared with FCL/Frac Er:Yag + normal saline injections in improvement of scars were statistically significant in studies by Lee *et al.*,¹⁵ Gawdat *et al.*,¹⁶ Shah *et al.*,¹⁸ Min *et al.*²⁰ and El-Taieb *et al.*²⁵ Abdel al *et al.*²² and El-Hawary *et al.*²⁹ observed significant improvement in FCL + PRP group as compared to platelet-rich plasma alone. But, El-Hawary *et al.*²⁹ did not find a significant difference between FCL + PRP group as compared to the fractional CO₂ laser alone. Taweel *et al.*²³ compared the FCL + PRP injections with FCL+ CO₂ gas injections (carboxy therapy) and found significant improvement in facial halves treated with FCL + PRP injections. Only one randomised control trial by Faghihi *et al.*¹⁷ found no differences in improvement of acne scars in FCL + PRP injections as compared to FCL + NS injections. A randomised control trial by Mahamoud *et al.*²⁷ compared FCL + PRP injections with FCL + hyaluronic acid injections and found no statistically significant difference between the two. Comparing the adverse effects of platelet-rich plasma injections as compared to normal saline controls, most studies (Lee *et al.*,¹⁵ Gawdat *et al.*,¹⁶ Shah *et al.*,¹⁸ Min *et al.*,²⁰ Abdel Aal *et al.*²² and El-Hawary *et al.*²⁹) reported significantly less intensity of erythema, edema, crusting, downtime and post-inflammatory hyperpigmentation. However, two studies Gawdat *et al.*¹⁶ and El-Hawary *et al.*,²⁹ reported significantly increased pain in the FCL + PRP group as compared to FCL + NS. Taweel *et al.*²³ too found significantly more edema in the intradermal platelet-rich plasma group as compared to the intradermal CO₂ group. Lastly, Faghihi *et al.*¹⁷ observed

significantly greater intensity of erythema and edema in FCL+ PRP side as compared to the control side.

Comparing the studies using topical platelet-rich plasma in fractional CO₂ laser and comparing it with topical normal saline, only one randomised control trial by Abdel-Maguid *et al.*²¹ showed significant improvement on comparing FCL + topical PRP and FCL + topical NS. Galal *et al.*²⁴ reported improved outcome on FCL + topical PRP side but did not mention whether it was statistically significant as compared to FCL + topical NS side. Two randomised control trials, by Kar *et al.*¹⁹ and Arsiwala *et al.*,²⁶ found no significant difference in improvement comparing FCL + topical PRP and FCL + topical NS. On analysing the adverse effects in combination of fractional CO₂ laser and topical platelet-rich plasma, Kar *et al.*¹⁹ found significantly less erythema, swelling and pain on FCL + topical PRP side than that on the fractional CO₂ laser-only side. Galal *et al.*²⁴ concluded that patient satisfaction scores on reduction of erythema and pigmentation were higher for the sides that were treated with FCL + PRP as compared to fractional CO₂ laser alone. Arsiwala *et al.*²⁶ also concluded that immediate adverse effects (erythema, edema and pain), as well as long-term adverse effects (post-inflammatory hyperpigmentation, pain, erythema, acne. and secondary infection), were less in the subjects treated with FCL + topical PRP, but the difference was not statistically significant. Abdel-Maguid *et al.*²¹ who compared FCL + PRP on one side with FCL + NS on the other observed no significant difference in the duration of erythema, edema, crusting or post-inflammatory hyperpigmentation between the two sides.

Despite acne scars being a common condition, the number of studies qualifying for this review was low (16), as we included only the studies with higher levels of evidence. The studies analysed are heterogeneous in nature with differences in study protocols, number of sessions of platelet-rich plasma and/or lasers, type of lasers used and durations of follow-up.

Conclusion

Through this review, we analysed 16 randomised control trials and split-face studies where most reported statistically significant improvement in acne scars combining fractional lasers and intradermal platelet-rich plasma. While most of these studies also reported significantly less adverse effects in terms of erythema, edema, downtime and post-inflammatory hyperpigmentation on fractional laser + PRP side, some reported increased incidence of pain and edema. Comparing topical platelet-rich plasma with intradermal injections, there is only one study with significant improvement while two others observed no improvements as compared to topical normal saline. However, when compared to injectable platelet-rich plasma, topical platelet-rich plasma caused much less incidence as well as severity of adverse effects. We recommend combining fractional ablative lasers and intradermal platelet-rich plasma in the management of acne scars for increased efficacy and to reduce the

incidence of procedure related erythema, post-inflammatory hyperpigmentation and downtime.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors have confirmed that there was no use of artificial intelligence (AI)-assisted technology for assistance in writing or editing of the manuscript, and no images were manipulated using the artificial intelligence.

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