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Current art of combination therapy with autologous platelet-rich plasma for stable vitiligo: A meta-analysis

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Abstract

Presently, there is an explosion in various uses of platelet-rich plasma (PRP). Several trials comparing combination therapy with PRP vs monotherapy for vitiligo have been published. However, evidence-based information is not enough for making well-informed decisions. This study aimed to evaluate several combination therapy strategies for vitiligo. EMBASE, PubMed, Web of Science, Cochrane Library and Google Scholar databases were searched to identify randomised controlled trials comparing combination therapy with PRP vs monotherapy for vitiligo. Eleven studies with 670 cases were included. Compared with monotherapy, clinical improvement of repigmentation was significantly higher in 308-nm excimer laser combined with PRP (odds rate for response rate of 50%-100% repigmentation, 4.47; 95% CI, 2.47-8.10; $P < .00001$) and in fractional carbon dioxide laser combined with PRP (mean difference for mean improvement grades of repigmentation, 1.61; 95% CI, 0.24-2.99; $P = .02$), respectively. Compared to monotherapy, there is no higher clinical improvement in strategies of PRP combined with narrowband-ultraviolet B or non-cultured epidermal cell suspension. Trivial adverse events were reported. This meta-analysis summarises current evidence that PRP combined with 308-nm excimer laser or fractional carbon dioxide laser is effective and safe for vitiligo. This systematic review and meta-analysis aims to evaluate the effectiveness and safety of several combination therapy strategies with PRP in the treatment of vitiligo. The response rate of repigmentation and mean improvement grades of repigmentation were mainly used for qualitative assessment. PRP combined with 308-nm excimer laser or fractional carbon dioxide laser is effective and safe for vitiligo due to its healing and regenerative properties.

KEYWORDS

combination therapy, excimer laser, fractional carbon dioxide laser, platelet-rich plasma, vitiligo

Jianguo Chen and Yingying Wan contributed equally to this article.

This systematic review and meta-analysis is registered under the name "Combination Therapy with Autologous Platelet-Rich Plasma for Vitiligo: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." PROSPERO registration number: CRD42020198075.

1 | INTRODUCTION

Vitiligo, a depigmentation disease characterised by epidermal melanocytes death and melanin loss,[1]

affects less than 0.1% to greater than 8% of the world's population,[2] and exerts cosmetic and psychosocial damage impacts. The treatment of vitiligo remains challenging for both dermatologist and aesthetic plastic surgeons. To data, there are some treatment modalities, such as topical steroids, topical calcineurin inhibitors, excimer laser, fractional carbon dioxide laser (FCL), narrowband–ultraviolet B therapy (NB-UVB), vitamin D, and non-cultured epidermal cell suspension (NCES), with the ultimate goal of skin repigmentation.[3] However, the treatment response is less satisfactory, probably due to polymorphisms in genes involved in the immune response and melanogenesis,[4] which may pave the way for combination therapy.

In the past decade, scientists have learned that the human body is an autogenous source of growth factors and fibrin clots. One of the representative autogenous regenerative biomaterials is platelet-rich plasma (PRP) that contains moderate to high concentration of platelets together with multiple biomolecules (eg, chemokines, growth factors, adhesive proteins, and cytokines) and moderate concentration of leucocytes.[5] Activated platelets can release autogenous growth factors that may initiate signalling cascades and lead to multiple intracellular changes, promoting the proliferation, migration and differentiation of stem cells and regulating local inflammation and immune responses.[5,6] Due to its healing and regenerative properties, PRP has been widely applied in the aesthetic and dermatology fields, involving facial rejuvenation, androgenic alopecia enrichment, chronic hard-to-heal skin ulcers healing, acne scars improvement, fat grafting enrichment, vitiligo, and melisma treatment as well.[7-11] Some studies also suggested that PRP could stimulate the proliferation of keratinocyte and fibroblasts, enhance interaction of keratinocyte and fibroblasts with melanocytes, and inhibit apoptosis of melanocytes.[12-14] Saify et al[15] conducted a pilot study and indicated that the single use of PRP for vitiligo could initiate repigmentation. These favourable outcomes have indicated that the PRP may be an effective adjuvant for vitiligo.

Recently, several studies have investigated the effect of the combination therapy with PRP on vitiligo. The combination therapy with PRP is quite new to us, and there are no consistent results regarding their efficacy and safety. Therefore, a systematic review and meta-analysis was conducted in our centre to evaluate the effects of the combination therapy with PRP and to provide reliable evidence for further clinical practice.

Key Messages

- This systematic review and meta-analysis aims to evaluate the effectiveness and safety of several combination therapy strategies with platelet-rich plasma in the treatment of vitiligo
- The response rate of repigmentation and mean improvement grades of repigmentation were mainly used for qualitative assessment
- Platelet-rich plasma combined with 308-nm excimer laser or fractional carbon dioxide laser is effective and safe for vitiligo due to its healing and regenerative properties

2 | MATERIALS AND METHODS

2.1 | Search strategy

The systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] Databases, including EMBASE, PubMed, Web of Science, Cochrane Library, and Google Scholar, were searched to identify randomised controlled trial comparing combination therapy with PRP to monotherapy without PRP for vitiligo, without restrictions of language, publication status, and publication year. The search terms were as follows: "platelet-rich plasma", "platelet concentrates", "platelet-rich gel", "PRP", "vitiligo", and "leukoderma". Reference lists of eligible studies and reviews were also searched for potentially relevant articles.

2.2 | Eligibility criteria

The inclusion criteria were as follows: (a) types of study: published randomised controlled trials; (b) types of participants: patients with vitiligo; (c) types of interventions: patients in intervention group underwent combination therapy with PRP (eg, excimer laser, FCL, NB-UVB, or NCES combined with PRP), and patients in the control group underwent monotherapy without PRP; (d) types of outcome measures: primary outcome includes response rate of repigmentation or mean improvement grade for repigmentation. Secondary outcomes include patient satisfaction and adverse events.

We excluded studies if they (a) were a study with fewer than 10 patients in each group; (b) were not randomised controlled trials (eg, retrospective studies, reviews, comments, letters, and guidelines); (c) had a follow-up duration with fewer than 1 month; and (d) did not document any outcome measures.

2.3 | Study selection

Two authors (J. C. and Y. W.) screened all the titles and abstracts of acquired studies independently. Then, potentially relevant full-text articles were assessed according to the eligibility criteria. Any discrepancies were resolved through discussion with another author (H. J.).

2.4 | Data abstraction and quality assessment

Baseline data of eligible studies were extracted using a standard form, including first author, publication year, study designs, number of participants, characteristics of vitiligo (subtype, duration, areas, anatomic sites), details of interventions and comparison, follow-up duration, outcomes, and PRP preparation protocols. Risk of bias was independently evaluated by two authors (J. C. and Y. W.) using the Cochrane tool, in terms of random sequence generation, allocation concealment methods, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other bias.[17] Any discrepancies between reviewers were resolved through discussion with another author (H. J.).

2.5 | Statistical analysis

All calculations were conducted using the Review Manager Software (RevMan 5.3). Mean difference (MD) with 95% confidence interval (CI) was calculated for continuous data and odds ratios (OR) with 95% CI for dichotomous data. Heterogeneity was assessed using an I^2 statistic. A fixed-effects model was used when I^2 was less than 50%. A random-effects model was adopted when I^2 was more than 50%, and heterogeneity was significant. $P < .05$ was considered to be statistically significant. Subgroup analysis was conducted according to different types of combination therapy with PRP. We also planned to carry out sensitivity analyses to explore the impact of an individual study by removing one study each time.

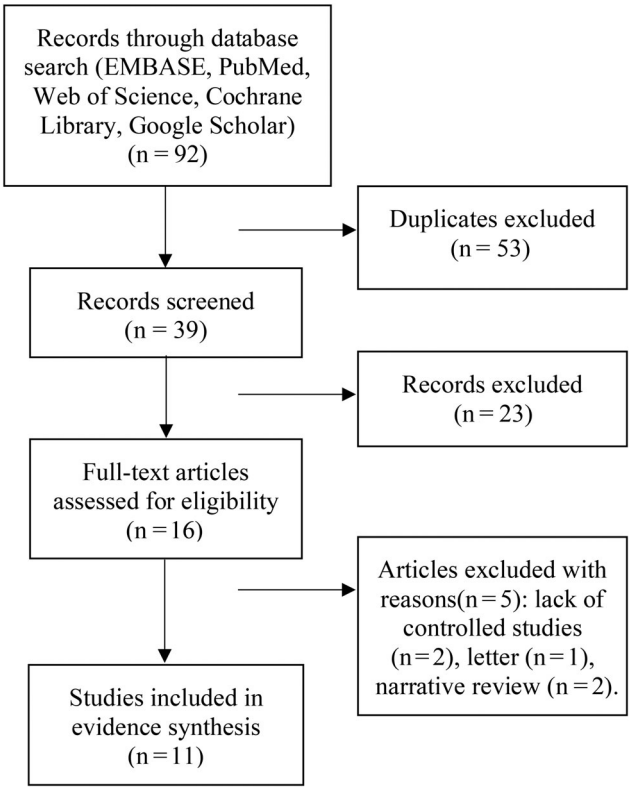

FIGURE 1 Flow diagram of study selection

3 | RESULTS

3.1 | Search results

The initial search yielded 92 studies, and 53 duplicated studies were excluded. The screening process excluded 23 studies based on the eligibility criteria. After reviewing the full texts, 5 studies were excluded for reasons: lack of controlled studies (n = 2), letter (n = 1), and narrative review (n = 2). Finally, 11 randomised controlled trials[12,13,18-26] with 670 cases (490 patients) were eligible for systematic review and meta-analysis (Figure 1). Of these cases, 337 cases belonged to combination therapy group and 333 cases were included in monotherapy group.

3.2 | Characteristics and quality of included studies

The characteristics of the included studies are shown in Table 1. In total, 670 cases (490 patients) were enrolled in 11 eligible studies from 2015 to 2020[12,13,18-26,] with the sample size ranging from 20 to 60 cases in a single group. All the cases were stable vitiligo. Of the included studies, 4 studies[18-21] were eligible for the comparison between excimer laser combined with PRP and excimer laser alone, with the

TABLE 1 Basic characteristics of the included studies

Study	I	Case no. I/C (patient no.)	Treatment interval/ sessions for PRP	Treatment interval/ sessions for "A"	Follow-up duration	Adverse events (cases no. of I/C)
Deng et al[18]	EL + PRP	20/20 (40)	1 month/3	Twice a week/24	3 months	None
Khattab et al[19]	EL + PRP	26/26 (52)	3 weeks/6	Twice a week/32	3 months	Pain (6/0), erythema (0/4)
Le[20]	EL + PRP	24/60 (84)	1 week/NR	Once or twice a week/15	12 months	Pain (NR), recurrence (1/13)
Li et al[21]	EL + PRP	40/40 (40)	3 weeks/3	Twice a week/18	3 months	Pain (40/0), erythema (1/1)
Abdelghani et al[12]	FCL + PRP	20/20 (40)	3 weeks/4	Biweekly/4	3 months	Erythema (NR)
Kadry et al[22]	FCL + PRP	30/30 (30)	2 weeks/6	biweekly/6	3 months	Pain (7/10), hyperpigmentation (2/8), erythema (NR)
Mrigpuri et al[23]	NCES + PRP	25/25 (20)	NA	NA	16 weeks	None
Parambath et al[24]	NCES + PRP	20/20 (20)	NA	NA	3, 6 months	None
Ibrahim et al[13]	NB-UVB + PRP	60/60 (60)	2 weeks/8	Twice a week/16	3 months	Pain: 30, ecchymosis: 9
Kale et al[25]	NB-UVB + PRP	32/32 (64)	2 weeks/8	Biweekly/8	2, 4 months	Pain: 15/17, ecchymosis: 3/2
El-Raheem et al[26]	Vitamin D + PRP	20/20 (40)	1 month/3	1 month/3	3 months	None

Abbreviations: "A", EL, FCL, NCES, NB-UVB, or vitamin D; C, control; EL, excimer laser; FCL, fractional carbon dioxide laser; I, intervention; PRP, platelet-rich plasma; NA, not applicable; NB-UVB, narrowband-ultraviolet B; NCES, non-cultured epidermal cell suspension; NR, not reported.

follow-up duration ranging from 3 to 12 months. Two studies[12,22] compared FCL combined with PRP vs FCL alone, with a follow-up duration of 3 months. Two studies[23,24] compared NCES combined with PRP to NCES alone, with the follow-up duration ranging from 3 to 6 months. Two studies[13,25] compared NB-UVB combined with PRP to NB-UVB alone, with the follow-up duration ranging from 2 to 4 months. One study[26] compared vitamin D combined with PRP to vitamin D alone, with a follow-up duration of 3 months. Regarding study quality, Figure 2 shows the results of the assessment for the included studies.

3.3 | Excimer laser combined with PRP intradermal injection vs excimer laser alone

Four studies with 256 cases evaluated response rates of repigmentation at the end using a four-point grading scale ("excellent" for 75%–100% repigmentation, "good" for 50%–75%, "moderate" for 25%–50%, "mild" for <25%). Quantitative synthesis suggested that the response rate of 50%–100% repigmentation was significantly higher in combination therapy group than in monotherapy group (OR = 4.47; 95% CI = 2.47-8.10; $P < .00001$). As heterogeneity was low ($I^2 = 42\%$, $P = .16$), a fixed-effects model was used for this evaluation (Figure 3). Only one study documented the patient satisfaction degree using the 10-point visual analog scale (VAS, 0–10: 0 = not satisfied at all, 10 = completely satisfied), with higher patient satisfaction degree in combination therapy than in monotherapy group. A meta-analysis was not performed due to only one study included.

3.4 | FCL combined with PRP intradermal injection vs FCL alone

Two studies with 100 cases reported the mean improvement grade for repigmentation at the end using a four-point grading scale (grade 4 = excellent for 75%–100% repigmentation, grade 3 = good for 50%-75%, grade 2 = moderate for 25%-50%, and grade 1 = mild for <25%). Pooled results indicated that mean improvement grade was significantly higher in combination therapy group than in monotherapy group (MD = 1.61; 95% CI = 0.24-2.99; $P = .02$). A random-effects model was used for this evaluation for the substantial heterogeneity. Furthermore, two studies also documented the patient satisfaction degree between two groups using the 10-point visual analog scale (VAS, 0–10: 0 = not satisfied at all, 10 = completely satisfied). Quantitative synthesis suggested that the patient satisfaction degree was significantly higher in combination therapy than in monotherapy group (MD = 4.20; 95% CI = 3.36-5.04; $P < .00001$). As heterogeneity was low ($I^2 = 9\%$, $P = .29$), a fixed-effects model was used for this evaluation (Figure 4).

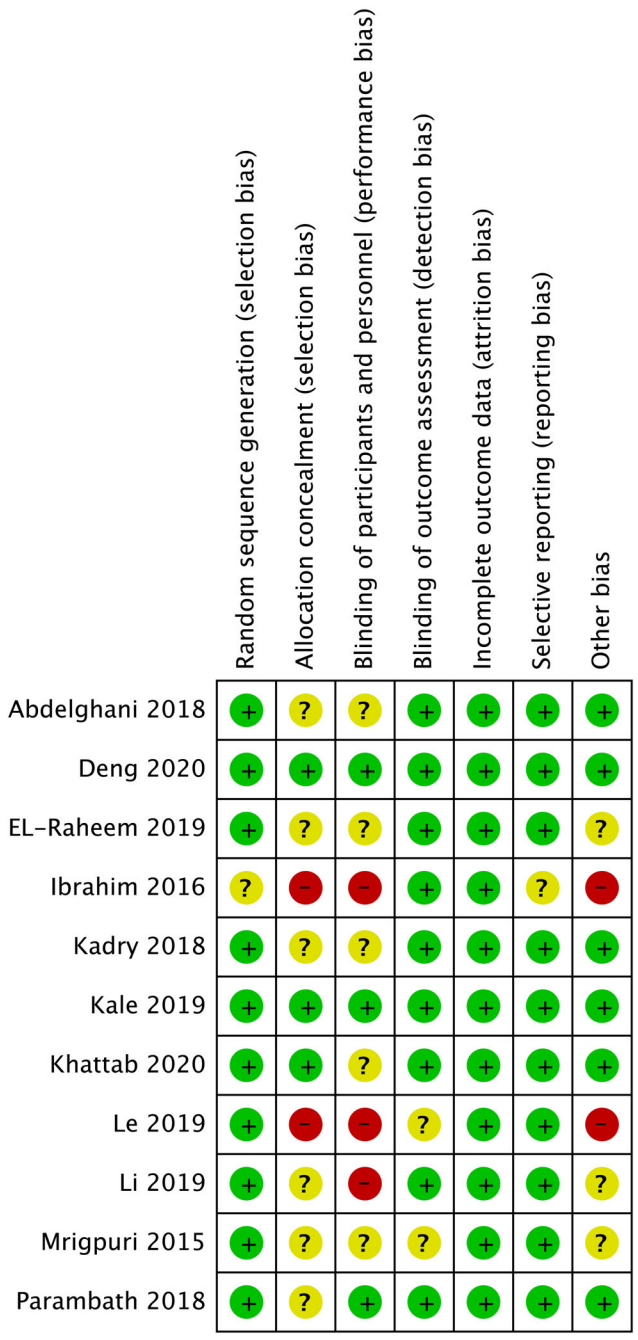

FIGURE 2 Risk of bias. Green circle = low bias risk; red circle = high bias risk; yellow circle = unclear bias risk

3.5 | NCES mixed with PRP vs NCES alone

Two studies with 90 cases evaluated response rates of repigmentation, using a six-point grading scale (grade 1 = 0%–25% repigmentation, grade 2 = 26%–50%, grade 3 = 51%–75%, grade 4 = 76%–90%, grade 5 = 91%–99%, and grade 6 = 100%). Quantitative synthesis suggested that no significant difference was seen between combination therapy and monotherapy in the response rates of repigmentation (OR = 1.00, 95% CI = 0.32-3.15, $P = 1.00$, for >75% repigmentation; OR = 2.17, 95% CI = 0.78-5.98, $P = .14$, for >90% repigmentation). No heterogeneity was found ($I^2 = 0\%$) and a fixed-effects model was used (Figure 5).

3.6 | NB-UVB combined with PRP intradermal injection vs NB-UVB alone

Two studies with 184 cases reported the response rates of repigmentation at the end using a four-point grading scale. Quantitative synthesis suggested that no significant difference was seen between combination therapy and monotherapy in the response rates of clinical improvement (OR = 4.12, 95% CI = 0.07-229.47, $P = .49$, for >50% repigmentation; OR = 16.57, 95% CI = 0.18-1503.09, $P = .22$, for >75% repigmentation) (Figure 6).

3.7 | Vitamin D combined with PRP injection vs vitamin D alone

One study evaluated the response rates of repigmentation using a four-point grading scale, and found that the clinical improvement in combination therapy was higher in vitamin D combined with PRP group than in monotherapy alone group. A meta-analysis was not conducted due to only one study included.

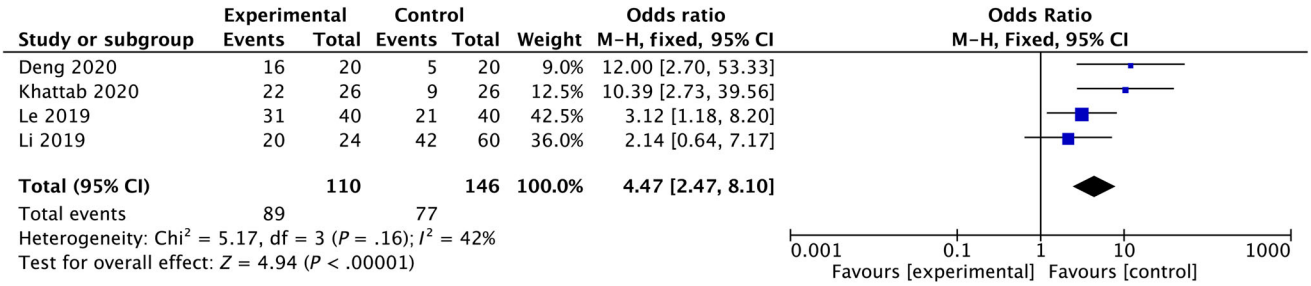

FIGURE 3 Response rate of 50% to 100% repigmentation (excimer laser combined with platelet-rich plasma vs excimer laser alone)

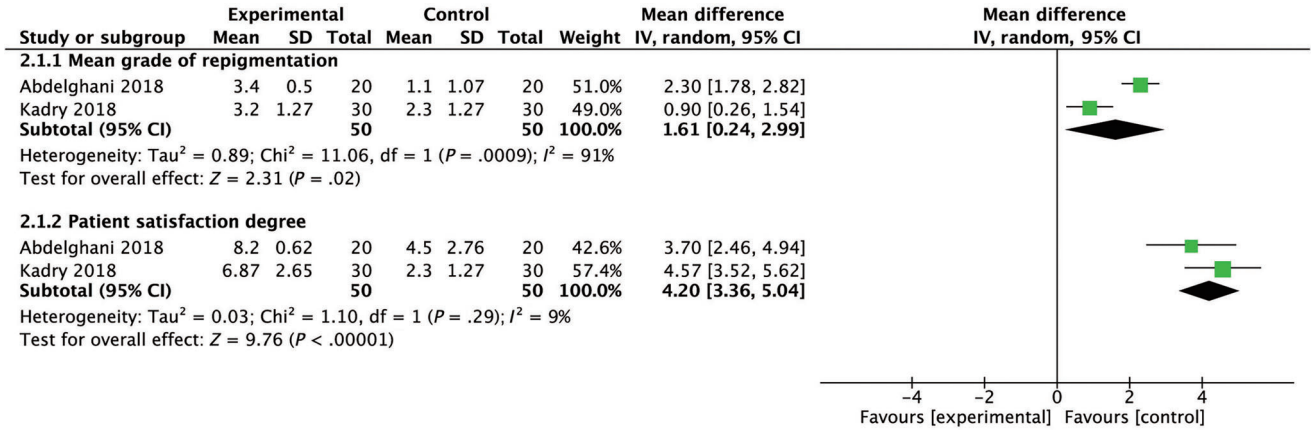

FIGURE 4 Mean improvement grades and patient satisfaction for repigmentation (fractional carbon dioxide laser combined with platelet-rich plasma vs fractional carbon dioxide laser alone)

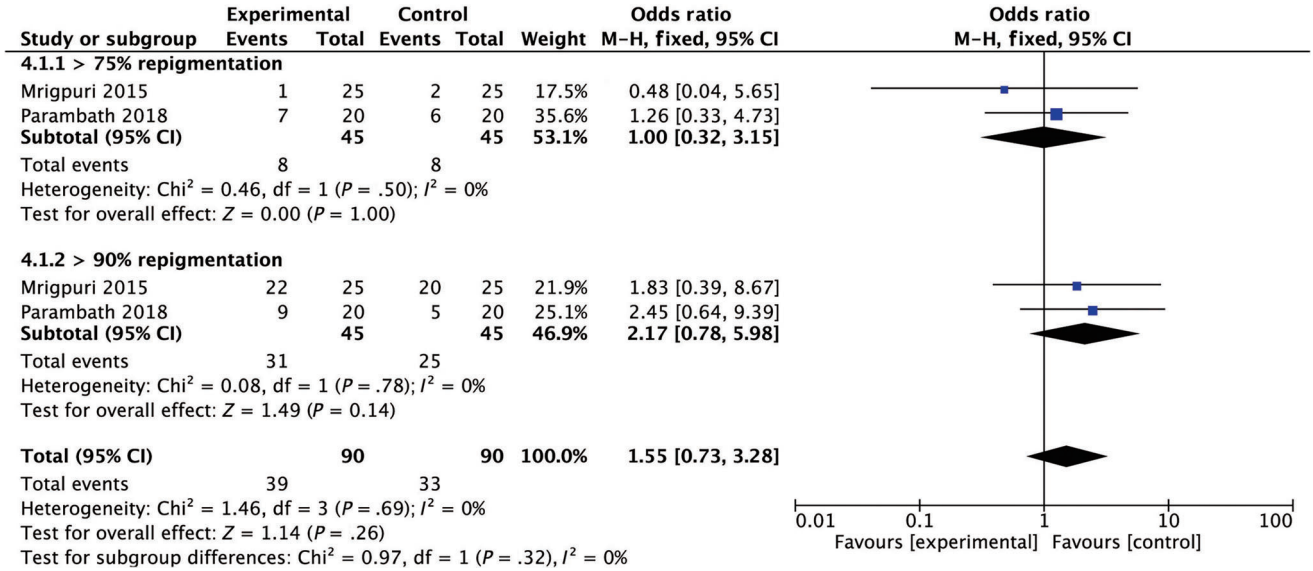

FIGURE 5 Response rates of repigmentation (non-cultured epidermal cell suspension combined with platelet-rich plasma vs non-cultured epidermal cell suspension alone)

3.8 | Trivial adverse events

Seven studies documented postprocedure adverse events, mainly including mild tolerable pain and erythema, which could be resolved without special treatment soon after they were reported. One study reported one case of recurrence in excimer laser plus PRP group while 13 cases were reported in monotherapy group. One study reported two cases of hyperpigmentation in FCL plus PRP group while 8 cases were reported in monotherapy group (Table 1).

3.9 | Sensitivity analysis

The sensitivity analyses suggested that none of studies qualitatively change the pooled results, confirming the robustness of the results.

4 | DISCUSSION

Vitiligo might affect patients' psychosocial health and quality of life, and the complex process of healing will increase medical expenses and induce significant distress in patients. In accordance with vitiligo's complex pathogenesis, there are miscellaneous treatment strategies, such as topical steroids, calcineurin inhibitors, janus kinase inhibitors, excimer laser, FCL, NB-UVB, vitamin D injection, and surgical techniques.[3,27-29] Due to the multifactorial and polygenic nature of the pathomechanism, none of these monotherapies was fully satisfactory. The European Dermatology Forum recommended NB-UVB/excimer laser combined with topical steroids, or topical immunomodulators,[30] while the Japanese Task Force recommended NB-UVB/photochemotherapy with UV-A combined with topical

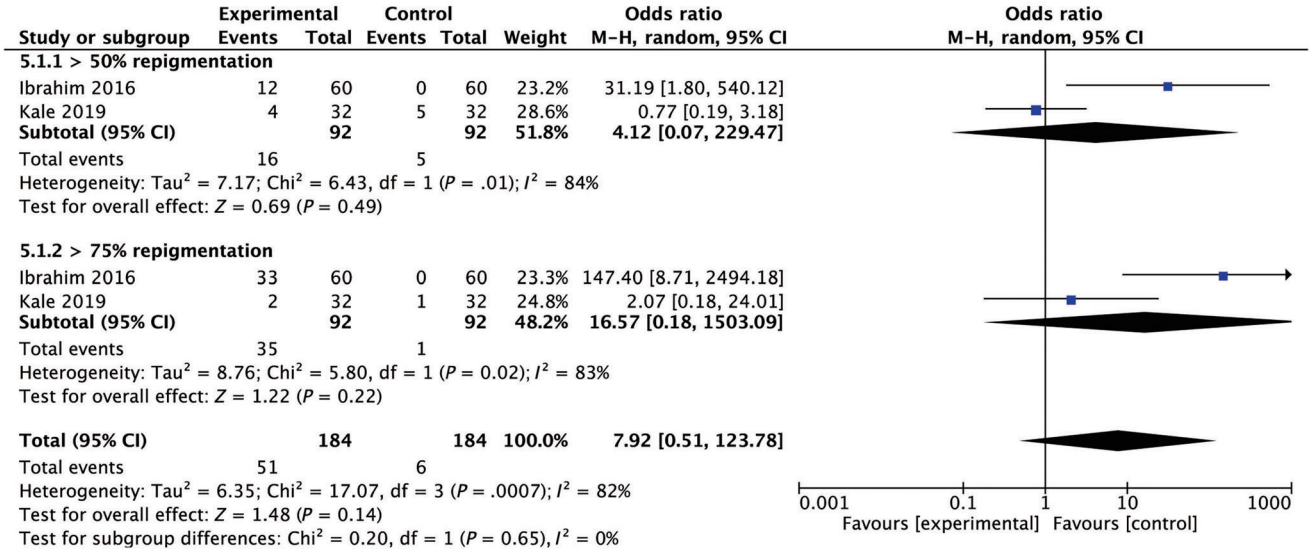

FIGURE 6 Response rates of repigmentation (narrowband–ultraviolet B combined with platelet-rich plasma vs narrowband–ultraviolet B alone)

steroids, or topical vitamin D as the important treatment for vitiligo.[31] However, the existing combination therapies may be associated with more adverse events.[32] It is, therefore, necessary to introduce other novel combination therapy regimens that are efficacious and safe for vitiligo.

The biology-oriented autologous PRP has been widely investigated in regenerative medicine due to its autologous source, safety, easy production, and the minimally invasive procedure. PRP contains multiple mitogenic/chemotactic growth factors (eg, vascular endothelial growth factor, transforming growth factor-β, platelet-derived growth factor, and insulin-like growth factor) together with moderate-to-high concentration of platelets and leucocytes trapped within the natural fibrin clots.[33] Furthermore, leucocytes may be another origin of autologous growth factors, especially the platelet-derived growth factor and vascular endothelial growth factor.[34] Potential favourable effects of leucocytes may be attributed to their roles in tissue remodelling, antibacterial affects, and regulation of immune responses.[35] Topical application or intradermal injection of PRP allow biomolecules to be delivered to target tissues, which effectively regulate some essential functions in the local microenvironment: proliferation, migration, and differentiation of stem cells (eg, dermal fibroblasts, epithelial cells, and endothelial cells), new collagen and matrix formation, modulation of inflammatory and immune responses, and angiogenesis, as well as antimicrobial effects.[5,36-40] These healing and regenerative properties pave the way that PRP may be a potentially effective biomaterial in vitiligo treatment. Recently, some researchers have begun to combine PRP with several conventional treatments for vitiligo in comparison to monotherapy, but inconsistent results were reported. Since the publication of these studies, a meta-analysis is warranted to address this issue.

To our knowledge, this is the first meta-analysis comparing the combination therapy with PRP to the monotherapy without PRP in vitiligo treatment. PRP is quite new in the treatment of vitiligo with only 11 eligible randomised controlled studies from 2015 to 2020. These combination therapies include following regimens: excimer laser + PRP, FCL + PRP, NB-UVB + PRP, NCES + PRP, and vitamin D + PRP. Quantitative synthesis yielded some important and different results for these combination therapies.

Compared with excimer laser alone, the excimer laser combined with PRP was more effective in promoting repigmentation. One of the mechanisms of the excimer laser in vitiligo treatment might be the role in stimulating melanogenesis via the wnt/β-catenin signalling pathway.[41] However, after the excimer laser treatment, the response rate of >75% repigmentation was between 12.5% and 61% in different literature studies, indicating that the effectiveness of excimer laser alone for vitiligo might be less robust.[42] Similarly, both the clinical improvement and patient satisfaction was significantly higher in FCL combined with PRP group than in FCL alone group. Kadry et al[22] conducted a histopathological comparison between monotherapy and combination therapy, and it was found that prominent melanin pigmentation and marked expression of HMB45 were seen in both PRP alone group and FCL combined with PRP group. Similar histopathological outcomes were also seen

in the study by Khattab et al,[19] who carried out a histopathological comparison between two groups and found that superior outcomes might be attributed to the healing and regenerative properties of PRP.

In contrast, pooled results indicated that no significant difference was found in response rates of clinical improvement (>75% repigmentation and >90% repigmentation) between NCES mixed with PRP and NCES alone. Surgical treatment for vitiligo aimed to transplant melanocytes from the normal pigmented areas to the depigmented patches. The key is to improve the survival of melanocytes after transplant. Two randomised controlled trials reported adverse outcomes for the application of NCES mixed with PRP. Similarly, no significant difference was seen in clinical improvement (>50% repigmentation and >75% repigmentation) between NB-UVB combined with PRP and NB-UVB alone. Two randomised controlled trials also reported adverse outcomes for the application of NB-UVB combined with PRP. In conclusion, there is inadequate evidence to support the combined use of PRP after the treatment of NCES or NB-UVB.

To date, PRP is considered to be under investigational use and is not approved by the Food and Drug Administration for the treatment of vitiligo. The preparation protocols, ratio of PRP dosing to treated areas, and safety of PRP should be carefully documented in the literature. The preparation protocols and the ratio of PRP dosing to treated areas were varied in the included studies, which could result in discrepancies of clinical outcomes among literature studies mentioned earlier. There is no agreement on the standardised PRP preparation protocols and optimal product with a homogeneous concentration of platelets and growth factors. Actually, it is quite difficult to achieve this agreement. There are majorities of variables impacting the compositions of PRP, such as baseline characteristics of patients, volume of collected blood, centrifugation tube materials, methods of platelet activation, centrifugation forces, and types of commercial centrifuges.[33] To obtain reproducibility of results and to provide guidelines for clinical practice, we suggested the detailed description of PRP preparation protocols and the ratio of PRP dosing to treated areas should be thoroughly reported in the literature. In our study, only trivial adverse events such as mild tolerable pain and erythema were mostly documented during the intradermal injection of PRP. No infection, postprocedure scarring, or Koebner phenomenon occurred, and only one study reported a case of recurrence in a year. The facts preliminarily indicate the safety and biocompatibility of PRP in clinical practice.

Overall, this study systematically reviewed the literature on the use of combination therapy with PRP for vitiligo improvement as well as integrated the data of the available randomised controlled trials in a meta-analysis to provide more convincing evidence for clinical practice.

The results should be cautiously interpreted. First, some eligible studies did not clearly suggest the blinding of patients and allocation concealment process, which may increase the risk of bias. Second, we did not assess publication bias through a funnel plot because fewer than 10 studies included in every outcome. Third, there were some clinical variabilities between the studies, such as the characteristics of vitiligo (ie, anatomical sites of lesions, areas, and duration), vitiligo treatment regimens, follow-up duration, PRP preparation protocols, and dosing, which may cause the conclusion of our meta-analysis less robust. Fourth, the application of PRP for vitiligo treatment is new to us, with quite few eligible randomised controlled trials included for pooled results. Furthermore, few included studies assessed segmental vitiligo and children with vitiligo. Our systematic review only provides some preliminary conclusion on the application of combination therapy regimens for vitiligo. Finally, the improvement in cost-efficiency and quality of life was not evaluated in this study, which should also be considered when making clinical decisions. Further randomised controlled studies about the total expense and comparison with conventional treatment are warranted.

5 | CONCLUSION

To our knowledge, this is the first meta-analysis to evaluate the efficacy of combination therapy with PRP for vitiligo enrichment. It provides preliminary evidence that PRP combined with excimer laser or fractional carbon dioxide laser exerts synergistic positive effects on clinical outcomes for vitiligo. However, there is inadequate evidence to support the combined use of PRP after the treatment of narrowband–ultraviolet B, or non-cultured epidermal cell suspension, or vitamin D injection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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