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Review Article

Efficacy and safety of combination therapy of excimer laser/light and drugs for vitiligo: a meta-analysis

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Abstract: Background: Current vitiligo therapies require a long therapeutic procedure, and outcomes are often far from satisfactory. Combination therapies of 308 nm excimer laser/light and various drugs represent a new treatment strategy. We performed a meta-analysis to evaluate the efficacy and safety of the combination therapy for vitiligo. Methods: Relevant studies published before February 2016 were identified by searching PubMed, Embase, EBSCO, and ISI web of knowledge. The repigmentation rate (four levels: 0-25%, 26-50%, 51-75% and 76-100%) and side effect of the combination therapy were assessed using risk ratio (RR) and corresponding 95% confidence interval (95% CI). Results: A total of six clinical studies consisting of 235 vitiligo patients were identified. No significant differences were found in 26-50% and 51-75% repigmentation rates between the excimer laser/light alone group (RR=1.40, 95% CI: 0.91-2.15) and combination group (RR=0.98, 95% CI: 0.64-1.51). However, the excimer laser/light alone group was higher than the combination group in 0-25% repigmentation rate (RR=1.81, 95% CI: 1.13-2.91) but lower in 75-100% repigmentation rate (RR=0.45, 95% CI: 0.32-0.65). The incident of side effects were comparable: RR=0.70, 95% CI: 0.37-1.31. Conclusion: Our meta-analysis suggested that the combination therapy was more effective in treating vitiligo, promoted 75-100% repigmentation rate and reduced the 0-25% repigmentation rate, as well as providing similar safety profile as the excimer laser/light alone therapy. Due to the small sample size in the present study, well-designed clinical studies with large sample size should be performed in the future.

Keywords: Excimer laser, excimer light, vitiligo, drug therapy, meta-analysis

Introduction

Vitiligo is an acquired cutaneous hypopigmentary disorder affecting about 0.1-4% of the population [1]. The skin disease is characterized by the loss of melanocytes from epidermis and epidermal appendages. Vitiligo can run a rapidly progressive course or remain stationary. The disease is not harmful medically, but the appearance of skin may affect patients' psychological and emotional well-being, impacting the quality of life [2].

When epidermal and mucosal variants occur, phototherapy is a mainstay of vitiligo treatment, although varying rates of efficacy were found. There are various types of phototherapies, such as Narrowband (NB)-ultraviolet (UV) B, psoralen plus UVA, and xenon chloride excimer laser/light therapy (308-nm laser/night) that was approved by the US Food and Drug Administration for the treatment of vitiligo since 2007 [3]. 308-nm excimer laser/light treatment provided a faster onset of repigmentation and required fewer treatment sessions for a successful response, when compared with conventional phototherapy. It is currently considered as an treatment option for localized vitiligo [4]. The 308-nm excimer laser has similar biological and clinical effects with NB-UVB; in addition, it can be used to treat small, non-accessible or resistant areas [5].

Several published clinical studies [6-9] have been conducted to investigate the efficacy and safety of drugs in combination with 308-nm excimer laser/light for treatment of vitiligo, but the results were inconsistent and controversial. In order to overcome the limitation of a single study, we performed this meta-analysis to provide a more comprehensive estimation of the efficacy of using 308-nm excimer laser/light alone or in combination with topical agents for vitiligo.

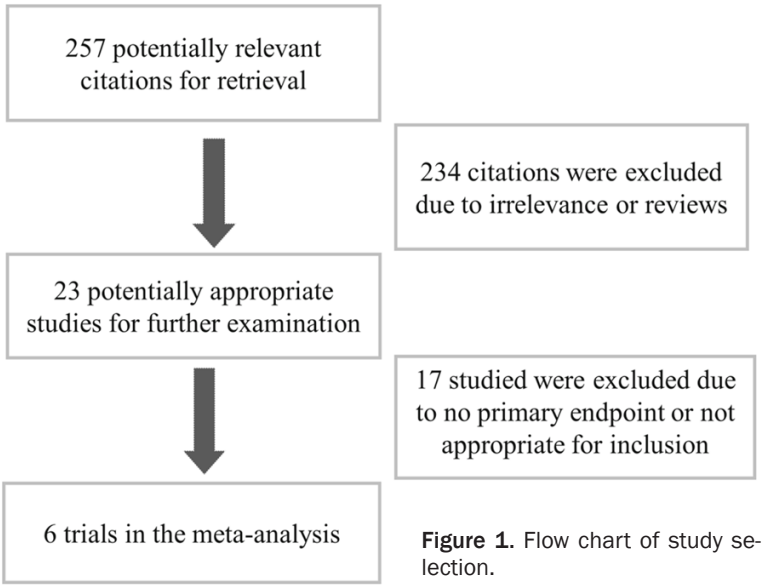

Figure 1. Flow chart of study selection.

Methods

Search strategy

Several databases, PubMed, Embase, EBSCO, and ISI web of knowledge, were used to retrieve studies on efficacy and safety of the 308-nm excimer laser/light for treatment of vitiligo published prior February 2016. Searching terms included: "vitiligo", "topical", "phototherapy", "excimer", "laser", "ultraviolet", and "UVB". Moreover, we searched the reference lists of retrieved articles to identify other relevant studies.

Inclusion and exclusion criteria

We performed initial screening on titles and abstracts, and the second screening on the full-text. Studies were considered eligible if they meet the following criteria: (1) it was a prospective randomized, controlled study; (2) It evaluated the efficacy and safety profile of 308-nm excimer laser/light for treatment of vitiligo.

The following studies were excluded: (1) studies without primary efficacy and safety data; (2) data came from reviews and abstracts; (3) repeatedly published literature.

Data extraction

Two reviewers independently searched and selected literatures. Relevant data were then extracted according to a data extraction form. Further discussion and assessment were performed among the reviewers to resolve disagreements on the extracted data. The extracted data include: the first author, year of publication, country of origin, sample size, source of control in control group.

Outcomes

The primary outcome measures were repigmentation rate (four level: 0-25%, 26-50%, 51-75% and 76-100%) and side effect. The clinical effective rate was defined as repigmentation rate higher than 25%.

Statistical analysis

Relative risk (RR) and their corresponding 95% confidence intervals (CIs) were used to evaluate the repigmentation rate and side effect between the two groups. Heterogeneity among the studies was checked by chi-square-based Q test and I^2 test. If the data showed no heterogeneity (P>0.10, I^2<50%), Mantel-Haenszel fix effect model was used, otherwise DerSimonian-Laird random effect model was used. Sensitivity analyses were conducted by omitting individual studies sequentially. Data were analyzed using STATA 11.0 SE (Stata Statistical Software, College Station, TX, USA, www.stata.com) software. To avoid risk of bias, we included only the randomized, controlled trials and excluded observational, dual submissions and follow up studies.

Results

Literature search

257 relevant studies were obtained from the databases. Of these, 234 were excluded during the primary screening on their title and abstract. The full-texts of the remaining 23 articles were reviewed by two independent investigators, and 17 articles were excluded as the inclusion criteria were not fulfilled. The remaining 6 articles [6-11], consisting of 235 vitiligo patients, were included in the meta-analysis. The screening process is illustrated in **Figure 1**.

Table 1. Characteristics of the selected randomized controlled trials (RCTs) in the analysis

Study	Treatment	Reference lesions	Age	Duration of disease (years)	Country	Treatment duration	Sample size	Score
Tang 2006	Tacalcitol +MEL1/MEL1	Face and neck, Trunk, Extremities	6-65	0.25-20	China	12 sessions	38	4
Goldinger 2007	MEL2+ calcipotriol/MEL2	Patients with skin type III-IV	2-60	/	Switzerland	24 treatments	10	4
Sassi 2008	MEL2+ hydrocortisone/MEL2	Face and neck	18-75	/	Italy	12 weeks	84	5
Yang 2009	MEL2+ pimecrolimus/MEL2	Face, trunk, finger	6-14	1.31 ± 0.50	China	30 weeks	49	4
Nistico 2012	MEL1+ tacrolimus/MEL1	Fitzpatrick skin type (I-V)	13-56	2.1	Italy	12 weeks	40	5
Passeron 2004	MEL2+ tacrolimus/MEL2	Fitzpatrick skin types II to IV	12-63	18.1	France	24 sessions	14	4

Note: MEL1: 308-nm excimer light, MEL2: 308-nm excimer laser.

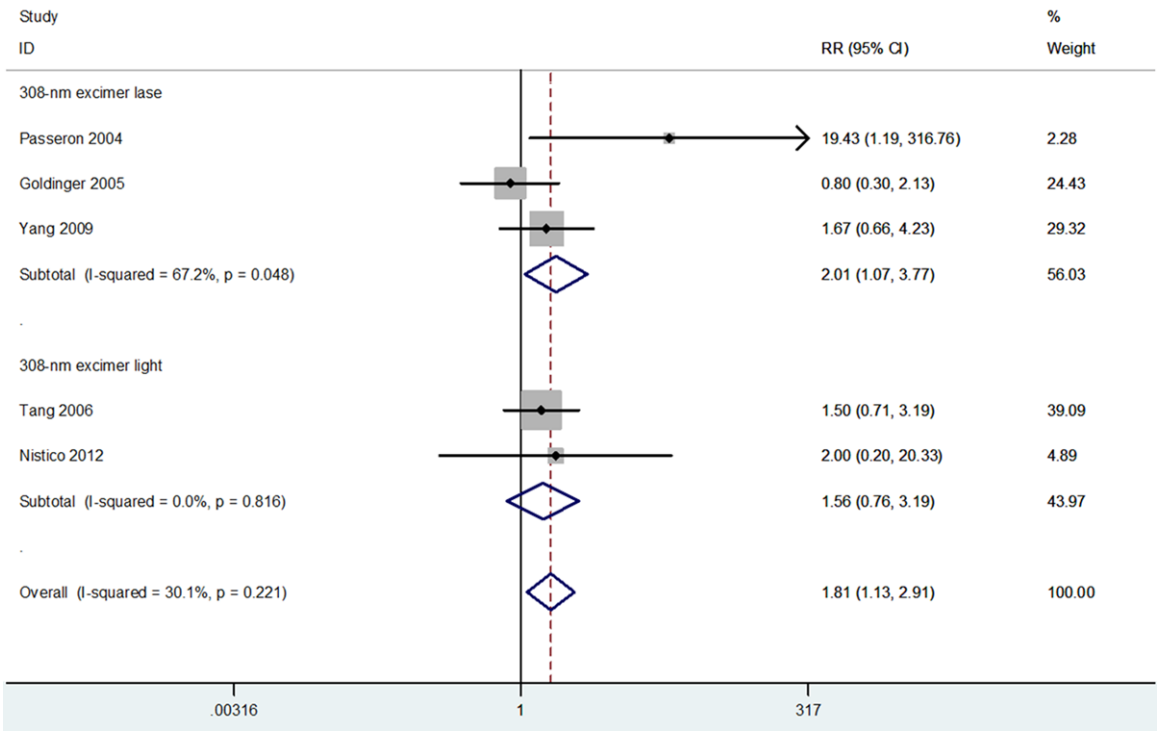

Figure 2. Forest plot with the fixed effects model in 0-25% repigmentation rate of two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

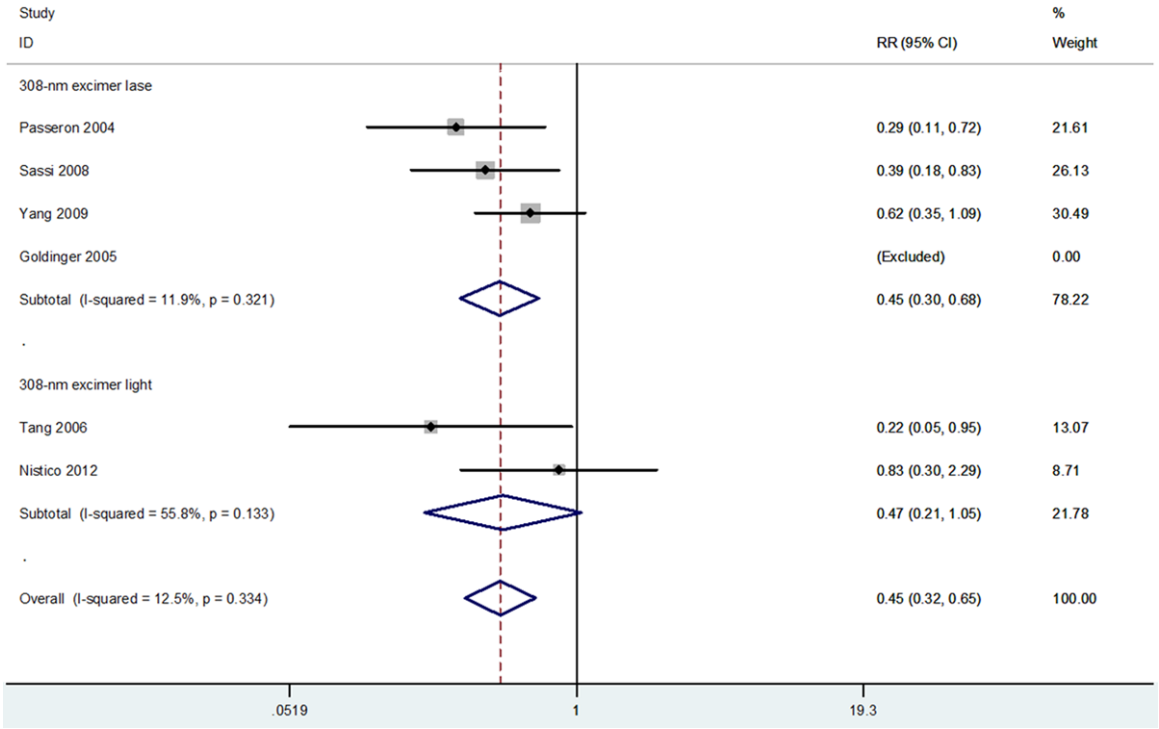

Figure 3. Forest plot with the fixed effects model in 75-100% repigmentation rate of two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

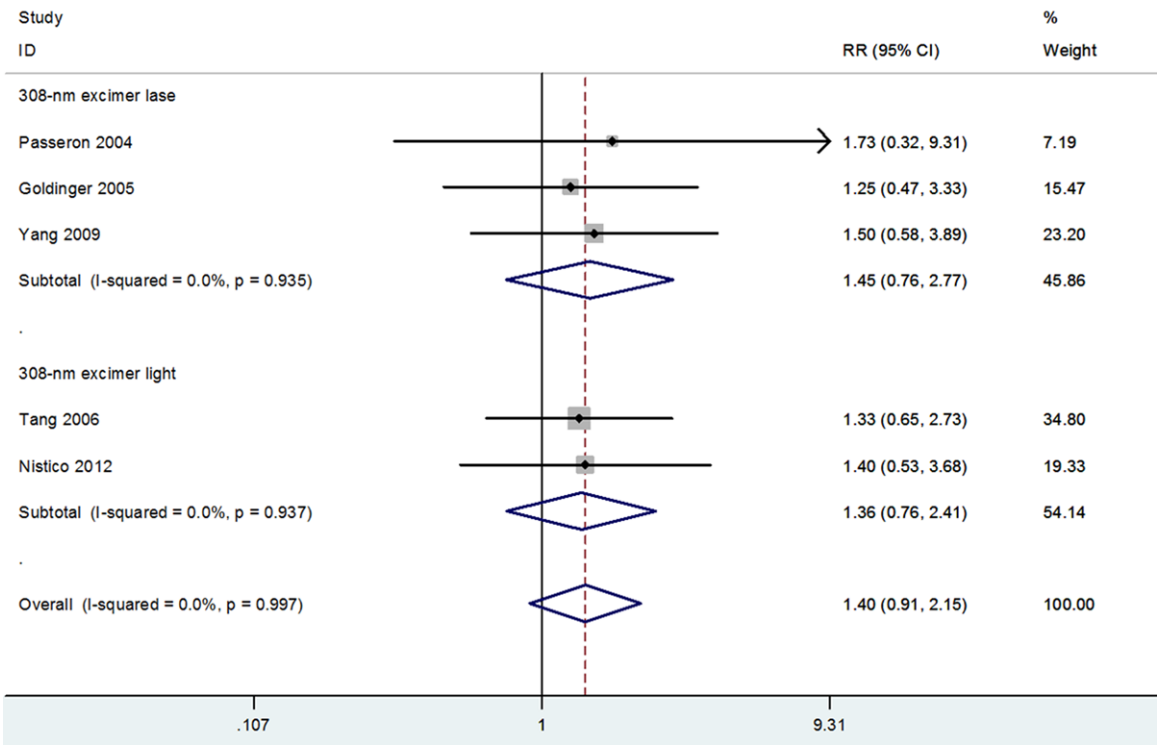

Figure 4. Forest plot with the fixed effects model in 25-50% repigmentation rate of two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

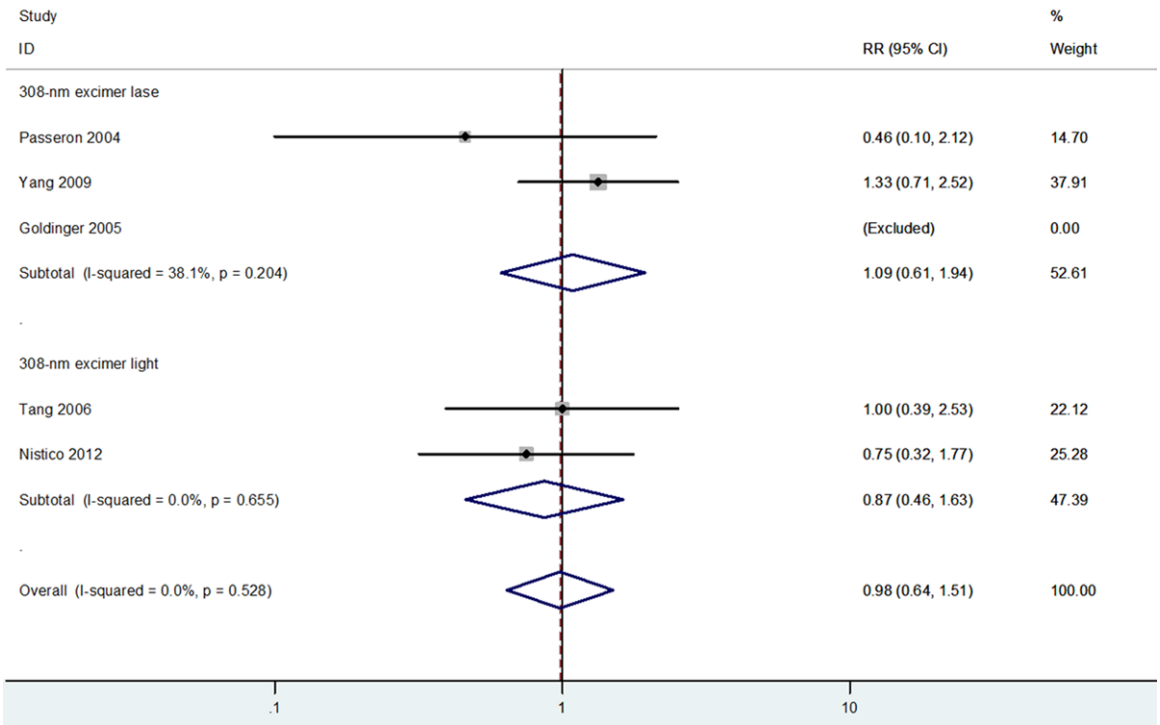

Figure 5. Forest plot with the fixed effects model in 50-75% repigmentation rate of two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

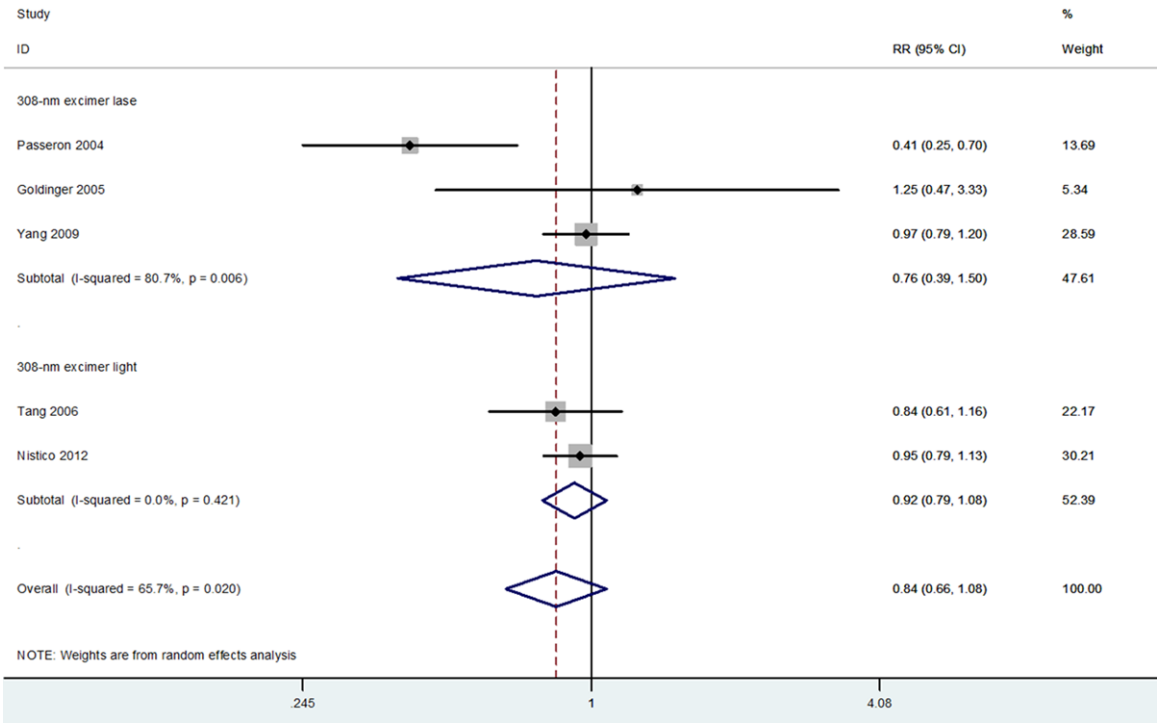

Figure 6. Forest plot with the random effects model in clinical effective rate (>25% repigmentation rate) of two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

Study characteristics

The characteristics of the included studies in this analysis were given in **Table 1**. All studies were published in high quality English journals (Modified Jadad score ≥4). Among these studies, 2 trials were conducted in Italy, 2 were in China, 1 was in France, and 1 was in Switzerland. Patients aged from 2 to 75. Reference lesions included Fitzpatrick skin type (I-V), such as face, neck, trunk, extremities.

Efficacy

Six clinical studies with a total number of 235 vitiligo patients were identified. As illustrated in **Figures 2** and **3**, the excimer laser/light alone group was higher than combination group in 0-25% repigmentation rate (RR=1.81, 95% CI: 1.13-2.91) but lower in the 75-100% repigmentation rate (RR=0.45, 95% CI: 0.32-0.65). No significant differences were found at 26-50% and 51-75% repigmentation rate between the excimer laser/light alone group and drug combination group: RR=1.40, 95% CI: 0.91-2.15; RR=0.98, 95% CI: 0.64-1.51, respectively (**Figures 4** and **5**). On the other hand, we performed a subgroup analysis, the results showed that the excimer laser and light were similar in efficacy and safety in treating vitiligo. We defined the clinical effective rate as higher than 25% repigmentation rate, and the two groups were parallel, RR=0.84, 95% CI: 0.66-1.08, as displayed in **Figure 6**.

Safety

The 6 trials recorded the safety of the two groups. The treatment duration varied from12 sessions to 30 weeks. The pooled analysis of treatments was illustrated in **Figure 7**. In general, no significant differences were found between the two treatment groups in the incident of side effect (RR=0.70, 95% CI: 0.37-1.31). Efficacy and safety indicators were summarized in **Table 2**.

Sensitivity analysis

Sensitivity analyses were conducted by omitting individual studies sequentially. The results did not change under some conditions, and the

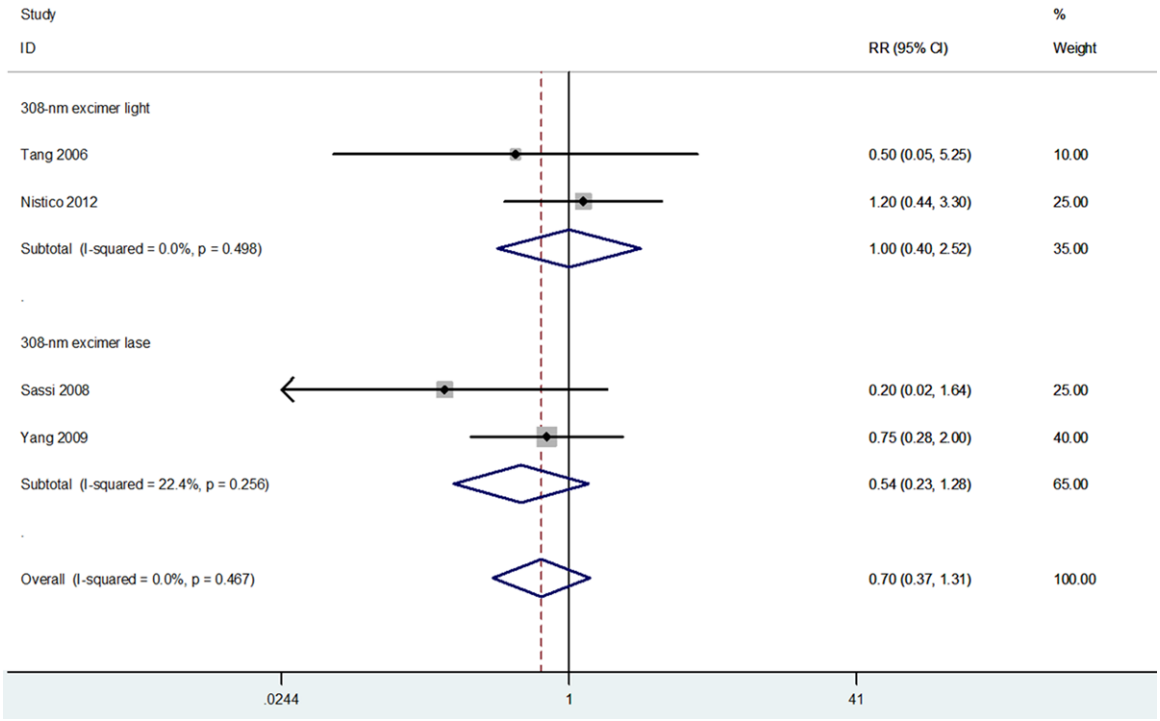

Figure 7. Forest plot with the fixed effects model of side effect in two groups. Risk ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at RR=1 indicates significance.

Table 2. Summarized results of this meta-analysis

Repigmentation Rate	RR	95% CI
0-25%*	1.81	1.13-2.91
25-50%	1.40	0.91-2.15
50-75%	0.98	0.64-1.51
75-100%*	0.45	0.32-0.65
>25%	0.84	0.66-1.08
Side Effect	0.70	0.37-1.31

RR: risk ratio; CI: confidence interval, *significant differences between excimer laser/light alone group versus combination group.

indicators for heterogeneity (I^2 and P_{het}) were reduced. Sensitivity study suggested that the results for vitiligo were stable and statistically robust.

Publication bias

No significant publication bias was observed.

Discussion

The present meta-analysis was conducted to investigate the effect of drug in combination with 308 nm excimer laser/light treatment. A total of 6 clinical trials were identified, and the data was pooled and analyzed. Overall, the combination group could promote the patients' clinical outcomes without additional side effect.

The pathogenesis of vitiligo remains elusive, but autoimmune dysfunction is one of the main hypotheses. 308-nm excimer laser/light treatment could help repigmentation by enhancing the migration and proliferation of melanocytes, and may improve the immune response [12]. It is believed that inactive melanocytes in the outer root sheath of the hair follicles are stimulated to proliferate and migrate by radiation of the treatment, leading to repigmentation [13, 14]. Excimer laser or light was recently introduced to give accurate, targeted treatment of vitiligo [3, 15]. However, monotherapy of excimer laser or light is not effective in all patients with vitiligo, the combination treatment strategy with topical remedies was suggested. The outcome of the combination treatment is controversy. We thus conducted this analysis to evaluate the two treatment strategies.

There was a systematic review on the treatment of 308-nm excimer laser for vitiligo [16]. It was conducted in 2012 and included 10 studies involving 411 patients. In the systematic review, the conclusions were that that the combination of 308-nm excimer laser with 0.03%-0.1% tacrolimus ointment or with thymosin injection could reduce the invalid rate of vitiligo, and the combination of 308-nm excimer laser with 0.1% tacrolimus or with tacalcitolointment improved the 75% repigmentation rate. Another systematic review, by Bae et al. [17], compared the efficacy of combination therapy of 308-nm excimer laser/light and topical agents with monotherapy for vitiligo. The study is similar to our meta-analysis; however, we had different inclusion and exclusion criteria, and different definition of clinical outcomes. In addition, we performed subgroup analysis within the excimer laser and light. In our systematic review, we focused on the comparison between combination therapy (308-excimer laser/light with drug) and monotherapy. The drugs included tacalcitol, calcipotriol, hydrocortisone, pimecrolimus and tacrolimus. Overall, the drugs could promote the therapeutic effect and clinical outcomes. Subgroup analysis showed no differences between the excimer laser and light in efficacy or safety profile.

In conclusion, our meta-analysis showed that the combination therapy of excimer laser/light with drug provided better clinical outcomes than monotherapy for the treatment of vitiligo. The combination therapy could significantly promote 75-100% repigmentation rate with satisfactory safety profile. Limitations, like sample size, may affect the analyses. Future studies with high methodological quality and large sample size are needed to further evaluate the clinical benefits of combination therapy of 308-nm excimer laser/light and drug for treating vitiligo.

Disclosure of conflict of interest

None.

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