Treatment of 308-nm excimer laser on vitiligo: A systematic review of randomized controlled trials

Yan Sun, Yan Wu, Bihuan Xiao, Lu Li, Li Li, Hong-Duo Chen, and Xing-Hua Gao

Department of Dermatology, No. 1 Hospital of China Medical University, Shenyang, China

Abstract

Background: Vitiligo is an acquired cutaneous hypopigmentary disorder, which characterized by solitary or multiple depigmented maculae or patches. The 308-nm excimer laser has been used as phototherapy on vitiligo. Objective: To evaluate the efficacy and safety of 308-nm excimer laser on vitiligo. Methods: Randomized controlled trials were searched to conduct a systematic review. The keywords were identified as laser/excimer laser/quasimolecule/XeCl'' and “vitiligo”. Results: Seven studies with 390 vitiligo patients were included. No significant differences were seen between 308-nm excimer laser and 308-nm excimer lamp on either ≥75% or ≥50% repigmentation rate, or between 308-nm excimer laser and narrowband-ultraviolet B (NB-UVB) on either 100% or ≥75% re-pigmentation rate. More patients or lesions achieved ≥50% repigmentation rate by 308-nm excimer laser treatment than by NB-UVB treatment. The side effects of 308-nm excimer laser were slight and tolerable. Conclusions: The 308-nm excimer laser showed equivalent efficacies to 308-nm excimer lamp control and NB-UVB control concerning ≥75% re-pigmentation rate of vitiligo patches. More studies with high methodological quality, low risk of bias and more sample size are needed to confirm the conclusion.

Introduction

Vitiligo is an acquired cutaneous hypopigmentary disorder affecting about 0.1–4% of the population, characterized by loss of melanocytes from the epidermis and the epidermal appendages. The exact pathogenesis remains unknown, although several contributing mechanisms have been implicated, including genetic, autoimmune, biochemical factors, oxidative stress and neural or viral causes (1). Its clinical presentation is characterized by solitary or multiple depigmented maculae or patches that may arise in a localized, segmental or generalized distribution. The disease is not harmful, but may cause psychological damage and has a great impact on the quality of life (1,2).

A variety of treatment regimens are currently employed to repigment the skin, such as topical and systemic immunosuppressants (3), topical or oral corticosteroids (4), surgery, phototherapy, etc. Conventional phototherapies include oral or topical psoralens plus ultraviolet A radiation, broadband ultraviolet B radiation and narrowband UVB (NB-UVB). In the past decades, an increasing number of reports have highlighted the value of the 308-nm excimer laser (5,6). The 308-nm excimer laser was first described for the treatment of vitiligo in 2001 (7), and US Food and Drug Administration has approved it for the treatment of vitiligo. The 308-nm excimer laser has similar biological and clinical effects with NB-UVB and has the advantage of enabling the treatment of small, non-accessible or resistant areas when compared to ordinary phototherapies (8).

Methods

Data sources and searches

Electronic databases including PubMed, Embase, CBMdisc, CNKI, Wanfang and CQVIP (up to August 2014) were searched to collect RCTs, without language limitation. The keywords were identified as “laser/excimer laser/quasimolecule/XeCl” and “vitiligo”. We also performed a manual search of the reference lists of identified articles to identify and retrieve relevant research studies.

Study selection

Two independent reviewers screened titles and abstracts of relevant articles for possible inclusion. If they disagreed with each other, full texts were downloaded, and even more, a third reviewer resolved. To be included in the review, a study must have 308-nm excimer laser therapy in the treatment group and other phototherapy (such as excimer lamp, NB-UVB) in the control group. Case report, clinical trial without control group, review or asking help for a third reviewer. Information extracted from each selected article included the first author, year of publication, characteristics, interventions, efficacy and side effects. The criteria recommended by the Cochrane Collaboration Handbook was used to assess the

Data extraction and assessment of risk of bias

Two reviewers independently extracted data and assessed bias risk of the included studies. Disagreements were resolved by discussion or asking help for a third reviewer. Information extracted was as follows: first author, year of publication, characteristics, interventions, efficacy and side effects. The criteria recommended by the Cochrane Collaboration Handbook was used to assess the
methodological quality of included trials. It mainly focused on description of random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting and other bias. The judgment for each entry was based on the answer of a question, with ‘‘High’’ indicating ‘‘high risk of bias’’, ‘‘Low’’ indicating ‘‘low risk of bias’’ and ‘‘Unclear’’ indicating ‘‘either lack of information or uncertainty over the potential for bias’’ (9).

Outcomes measurement
The primary outcomes was 100%, ≥75% or ≥50% re-pigmentation rate. The secondary outcomes were the cumulative UV dose, the re-pigmentation scores and side effects.

Data synthesis
The meta-analysis was performed by Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We used relative risk (RR) for dichotomous data, considering a confidence interval of 95% by fixed effects model and forest plots were generated. Statistical heterogeneity was considered if $p<0.10$ for the chi-square test and $I^2>50\%$, and the potential factors that influenced this phenomenon were investigated in those cases. When studies were found to be moderately heterogeneous, the random effects model for calculation of RR’s was used and reported. $p<0.05$ was considered to be statistically significant. To ensure the reliability and accuracy of the results, two reviewers populated the data in the statistical software programs independently and got the same results.

Results

Eligible studies
A total of 695 potentially relevant studies were identified by a systematic bibliographic retrieval. After review of titles and abstracts, 591 non-relevant studies were excluded. The remaining 104 articles were screened full text for detailed evaluation to determine whether or not to accept in the analysis. Then corporate review excluded 97 studies not eligible. Finally, seven RCTs were reserved and included in the study (10–16). The procedure is illustrated in Figure 1.

Study characteristics
Among the seven RCTs, four were written in English and three were written in Chinese. The ethnicities of two studies were European and five were Asian. A total of 390 patients with vitiligo were included, no matter adult or children. The baseline characteristics of the studies are listed in Table 1.

Figure 1. The flow diagram of included studies.
### Intervention schemas

Three studies compared the efficacy and/or safety of 308-nm excimer laser with 308-nm excimer lamp (11,14,15), and four studies compared that of 308-nm excimer laser with NB-UVB (12,13,16,17). The interventions of included studies are listed in Table 2.

### Quality assessment

Random sequence generation was adequately performed in two studies (13,15). Allocation concealment, blinding of participants and personnel and blinding of outcome assessment were, respectively, described in three studies (11,13,15). Incomplete outcome data was conducted in six studies (11–15,17), selective reporting was conducted in six studies (10–13,15,16) and other bias were conducted in five studies (11–15). The risk of bias of the selected studies is shown in Figure 2.

### Efficacy evaluation

**The 100% re-pigmentation rate**

Two studies compared the number of patients who achieved 100% re-pigmentation rate between 308-nm excimer laser and NB-UVB (10,12). Meta-analysis under fixed effects model showed that there were no statistic significances between the two treatments (RR = 1.98 [0.84–4.67], p > 0.05; Figure 3).

**The ≥75% re-pigmentation rate**

Four studies were included for the evaluation (13–16). Amongst them, two studies compared the numbers of patients who achieved ≥75% re-pigmentation rate between 308-nm excimer laser and 308-nm excimer lamp. Meta-analysis under fixed effects model showed that there were no statistic significances between the two treatments (RR = 1.04 [0.77–1.42], p > 0.05). Another two studies compared the ≥75% re-pigmentation rate between 308-nm excimer laser and NB-UVB (13,16). One study expressed as no. of patients (13) and one presented as no. of lesions (16). Neither showed significant difference between the two treatments (RR = 0.67 [0.13–3.47], RR = 1.09 [0.85–1.40], p > 0.05; Figure 4).

**The ≥50% re-pigmentation rate**

There were four studies included for the evaluation (11,12,15,17). Two studies compared the number of lesions that achieved ≥50% re-pigmentation rate between excimer laser and 308-nm excimer lamp (11,15). Meta-analysis using fixed effects model showed no statistic significances between the two comparisons (RR = 1.00 [0.76–1.31], p > 0.05). Another two studies compared the number of patients (12,17) and one of the two (17) also compared the number of lesions between 308-nm excimer laser and NB-UVB. The results showed statistically significant between the two treatments (RR = 1.39 [1.05–1.85], RR = 1.41 [1.09–1.82], p < 0.05); more patients or lesions achieved ≥50% re-pigmentation rate by 308-nm excimer laser treatment than by NB-UVB treatment (Figure 5).

**The cumulative UV dose**

One study compared the cumulative UV dose of 308-nm excimer laser and NB-UVB (13). The cumulative UV dose of 308-nm excimer laser was lesser than that of NB-UVB (RR = −18.30 [−20.92 to −15.68], p < 0.05).

**The re-pigmentation scores**

Two studies compared the re-pigmentation scores between 308-nm excimer laser and 308-nm excimer lamp (11,14,15). The mean
Table 2. Interventions of included studies.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Laser treatment</th>
<th>Control</th>
<th>Frequency</th>
<th>Duration</th>
<th>Efficacy measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Duff et al. (10)</td>
<td>308-nm excimer laser (LIOS; Quantel Medical, France)</td>
<td>308-nm excimer lamp (Quantel Medical, Tokyo, Japan)</td>
<td>Two/week</td>
<td>24 sessions</td>
<td>≥50% (lesions)</td>
</tr>
<tr>
<td>Shi et al. (15)</td>
<td>308-nm excimer laser (PhotoMedex, Xtra)</td>
<td>308-nm excimer lamp (USHIO, Tokyo, Japan)</td>
<td>Three/week</td>
<td>20 sessions</td>
<td>≥75%, 50% (lesions)</td>
</tr>
<tr>
<td>Liu et al. (14)</td>
<td>308-nm excimer laser (Waldmann Co., Villingen-Schwenningen, Germany)</td>
<td>308-nm excimer lamp (PhotoMedex, Vtra)</td>
<td>Two/week</td>
<td>30 sessions</td>
<td>≥75% (lesions)</td>
</tr>
<tr>
<td>Yang et al. (16)</td>
<td>308-nm excimer laser (Waldmann Co., Villingen-Schwenningen, Germany)</td>
<td>308-nm excimer lamp (PhotoMedex, Vtra)</td>
<td>Two/week</td>
<td>20 sessions</td>
<td>100%, ≥50% (patients)</td>
</tr>
<tr>
<td>Linthorst et al. (13)</td>
<td>308-nm excimer laser (Talos; Wavelight Laser Technology AG, Erlangen, Germany) + punch grafting</td>
<td>Laser Technology AG, Erlangen, Germany + punch grafting</td>
<td>Two/week</td>
<td>3 months</td>
<td>≥75% (lesions)</td>
</tr>
</tbody>
</table>

The pathogenesis of vitiligo is still unclear nowadays, but autoimmune theory is more popular. The major mechanism of action of UVB light is enhancing the migration and proliferation of melanocytes resulting in re-pigmentation and a further impact on the immune response (22). In addition, UVB wavelength can activate the pseudocatalase complex, which is capable of degrading H2O2 and is associated with the successful re-pigmentation of vitiligo (23). The 308-nm excimer laser, 308-nm excimer lamp (peak wavelength 308-nm) and NB-UVB (peak wavelength 311-nm) are photobiologically very close. But 308-nm excimer laser and lamp are applied in a targeted way that allows the delivery of higher fluences to the lesion and spares the uninvolved skin resulting in more and faster re-pigmentation with less side effects (24,25).

The side effects

Six studies listed the side effects in their papers (11–15,17–20). The types, severity and number of side effects of 308-nm excimer laser were similar to those of 308-nm excimer lamp or NB-UVB. The most common side effects were erythema, itching, burning and blister, which were well tolerated. There was no severe side effect. The details are listed in Table 3.

Discussion

Seven studies were included in our systematic review. Although all the study mentioned “random”, only two studies adequately described the random sequence generation. Nearly 50% studies conducted allocation concealment, blinding of participants and personnel and blinding of outcome assessment. So the selection bias, performance bias and detection bias were moderately controlled. Over 85% studies reported the incomplete outcome data and conducted selective reporting, so the attribution bias and reporting bias were well controlled. Thus, the overall methodological quality of included studies was moderate.

There was one systematic review on the treatment of 308-nm excimer laser of vitiligo in literature (21). It was conducted in 2012 and included 10 studies (including RCTs and non-RCTs) involving 411 patients. In the systematic review, the control groups of seven studies were 308-nm excimer laser, one was NB-UVB (non-RCT), one was epidermis transplanting and one study compared the different intervals of 308-nm excimer laser. The conclusions were that the combination of 308-nm excimer laser with 0.03%–0.1% tacrolimus ointment or with thymosin injection can decrease the invalid rate of vitiligo, and the combination of 308-nm excimer laser with 0.1% tacrolimus or with tacalcitol ointment can improve the 75% re-pigmentation rate. In our systematic review, the included criteria and evaluation indicators were different from previous systemic review. We focused on the comparison between 308-excimer laser and other phototherapies including 308-nm excimer lamp and NB-UVB. The primary outcome was of 100%, ≥75% and ≥50% re-pigmentation rate. To assess the methodological qualities, we used the latest criteria recommended in the Cochrane Collaboration Handbook. Our review showed that no difference was seen between 308-nm excimer laser and 308-nm excimer lamp on the ≥75% and ≥50% re-pigmentation rate of vitiligo, as well between 308-nm excimer laser and NB-UVB on the 100% and ≥75% re-pigmentation rate. The results surprised us as the 308-nm excimer laser was ever expected to have better efficacy than the other phototherapies.

The pathogenesis of vitiligo is still unclear nowadays, but autoimmune theory is more popular. The major mechanism of action of UVB light (308-nm excimer laser, 308-nm excimer lamp and NB-UVB) in the treatment of inflammatory dermatosis is enhancing the migration and proliferation of melanocytes resulting in re-pigmentation and a further impact on the immune response (22). In addition, UVB wavelength can activate the pseudocatalase complex, which is capable of degrading H2O2 and is associated with the successful re-pigmentation of vitiligo (23). The 308-nm excimer laser, 308-nm excimer lamp (peak wavelength 308-nm) and NB-UVB (peak wavelength 311-nm) are photobiologically very close. But 308-nm excimer laser and lamp are applied in a targeted way that allows the delivery of higher fluences to the lesion and spares the uninvolved skin resulting in more and faster re-pigmentation with less side effects (24,25).
Figure 2. The methodological qualities of included studies.

Figure 3. The forest plots of 100% re-pigmentation rate.

Figure 4. The forest plots of ≥75% re-pigmentation rate.
As a newer phototherapy, they have the advantages of shortening the treatment and lessening the cumulative UV dose (24,26). And the light spot of 308-nm excimer laser is less than that of 308-nm excimer lamp, enabling easier of assess for small lesions. Theoretically, 308-nm excimer laser is better than 308-nm excimer lamp/NB-UVB as the laser is monochromatic. However, we are amazing to find that the efficacy is almost the same as the latter two phototherapies. The results should be verified in future studies.

There were some limitations in our systemic review. First, the publication bias was a concern in any systematic review. It was possible that studies suggesting benefits of the intervention of interest were published, while those of which results point in another direction remained unpublished. Second, the type, phase and location of lesions, and the frequency, duration and evaluation time-point of treatments of all the included studies were not consistent, which may cause an inherent bias. Third, the number of included study and the number of patients were relatively small, which will frustrate the final results.

In conclusion, the systematic review of seven RCTs demonstrated that 308-nm excimer laser showed equivalent efficacies to 308-nm excimer lamp control and NB-UVB control concerning of ≥75% re-pigmentation of vitiligo patches. As some limitations may undoubtedly affect our final conclusions, more studies with high methodological quality and more sample sizes are needed to determine the clinical benefits of 308-nm excimer laser in the treatment of vitiligo.

Declaration of interest
The authors have no commercial associations that might create a conflict of interest in connection with submitted manuscripts.

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References


