

Original Article

Efficacy evaluation of 585 nm pulsed dye laser in pathological scars

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Abstract: Objective: The 585 nm pulsed dye laser (PDL) is a widely used method for treating pathological scars in clinical practice. The present paper evaluated the efficacy and safety of 585 nm PDL in pathological scar. Method: PubMed, Cochrane Library, CNKI Database and Wanfang Database were searched for relevant data, and meta-analysis was performed for homogeneous trials using Revman 5.2 software. Results: Seven trials with a total of 268 scars were included. Analysis results showed that the Vancouver scar scale (VSS) scores in the group of 585 nm PDL were significantly superior to those of the blank control group. Although 585 nm PDL was generally effective for improving scars, no explicit evidence was gained on its efficacy in terms of scar size, erythema, pliability and hardness. Conclusion: The present study indicated that 585 nm PDL is safe and effective in treating pathological scars.

Keywords: 585 nm pulsed dye laser (PDL), pathological scar, efficacy evaluation, systematic evaluation, meta-analysis

Introduction

Pathological scars are common dermatological disease consisting of hypertrophic scars and keloids [1]. The main cause for pathological scars is believed to be excess dermal fibrosis due to cell function disorder during regulation of wound healing [2, 3]. So far the pathogenesis of pathological scar as a type of dermal tumor is still unknown [4]. Besides the sensations of itch and pain and psychological stress, pathological scars occurring to joints also bring about extremity dysfunction. Many techniques are applied to treat pathological scars [5], including surgical treatment, therapeutic irradiation, radioisotope therapy, pressure therapy, silicone therapy, cryotherapy, laser therapy and medication. But any of the above therapies used alone has limited effect. With a lack of controlled prospective trials [6], the efficacy and safety of most therapies are not sufficiently confirmed by evidence-based medicine. There is little guidance that clinicians can resort to when administering the treatment.

Alster et al. [7] first reported the use of flash-lamp-pumped pulsed dye laser (585 nm) in

1994 that improved the color and texture of hypertrophic scars after one or two treatments with a response rate of 57-83%. Since then many reports have been published on the application of 585 nm PDL in pathological scars with varying response rate [8, 9]. This technique has found extensive applications due to its convenience and invasiveness.

PDL is a vascular-specific laser that destroys scarred vessels via selective photothermolysis. Though believed to be a promising laser therapy [10], PDL can cause purpura of varying degree in nearly every patient. Purpura is usually transient and spontaneously disappears within 2 weeks but may reduce patient compliance according to some clinicians. It is of high necessity to evaluate the efficacy of 585 PDL using high-quality randomized clinical trials and to perform comparative analysis in terms of its safety with other therapies.

We adopted Cochrane methodology to carry out safety and efficacy evaluation and data analysis based on randomized or semi-randomized controlled trials concerning 585 nm PDL for pathological scars.

Materials and methods

Inclusion criteria

All the inclusion criteria should be following below:

Design of the trial: Randomized or semi-randomized controlled trials on 585 nm PDL consisting of blank control or other single therapy were included.

Subjects: Patients with hypertrophic scars or keloids.

Interventions: 585 nm PDL alone was administered for the treatment group. The control groups were divided into (1) blank control and (2) silicone therapy, pressure therapy, intra-lesional injection of cortical hormone, cryotherapy and other laser therapy (595 nm PDL) used alone.

Primary outcome measures: (1) Vancouver scar scale (VSS); (2) Erythema; (3) Size, pliability, softness and texture.

Secondary outcome measures: (1) Patients' subjective evaluation of the scars; (2) Improvement of itch and pain; (3) Other evaluation scales; (4) Other.

Exclusion criteria

The combined use of 585 nm PDL and other therapies (including other laser therapies and non-laser therapies) was excluded. Surgical treatment and comprehensive treatment were excluded.

Literature search

Cochrane Central Register of Controlled Trails (CCRT), MEDLINE Database, Embase, Chinese Biomedical Literature Database, Vendor Information Pages (VIP) Database and CNKI Database (1979 to 2014) were searched for relevant literature.

Screening of included trials

The titles and abstracts of the preliminarily included trials were reviewed by two researchers independently. For qualified trials the whole text was read to decide whether they conformed to inclusion criteria. Cross-checking was performed for the included trials. Divergence of opinions was resolved by discus-

sion between the two researchers or by consulting with the third party.

Quality evaluation

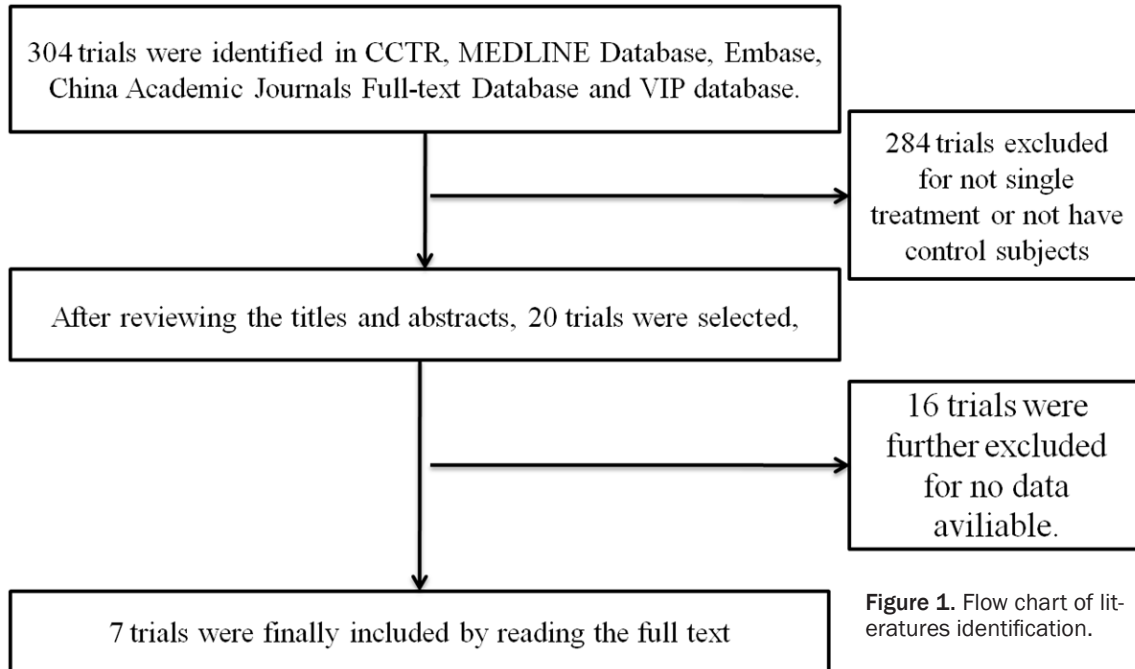
Cochrane Handbook for Systematic Reviews of Interventions (version 5.2) was used to evaluate the quality of the included trials by 2 researchers from four dimensions independently. Divergence of opinions was resolved by discussion or by consulting with the third party. Three quality levels were set up, namely, A, B and C.

Data extraction

Data extraction table was specifically designed for the current study. One researcher was responsible for data extraction and input, and the other for cross-checking. Divergence of opinions was resolved by discussion. The directors of the included trials were contacted for additional information. The extracted data covered the following aspects: (1) General information: name, author and site of trials; (2) Features of trials: type, subjects, baseline comparability and control inventions of trials; (3) Measurements: outcome measures, follow-up visits and adverse reaction report.

Data analysis

If the data available from the included trials were not fit for meta-analysis, descriptive analysis was performed instead. RevMan5.2 software was used for quantitative analysis. Clinical heterogeneity was evaluated in terms of age, scar type and course of disease of the subjects. Trials presenting with clinical heterogeneity were described separately. For trials showing no clinical heterogeneity, chi-square test was performed to detect statistical heterogeneity. If no statistical heterogeneity was found between the trials ($P \geq 0.1$, $I^2 \leq 50\%$), the fixed-effects model was adopted; otherwise, random-effects model was adopted. For categorical binary data, relative risk/risk ratio (RR) or odds ratio (OR) was calculated at 95% confidence interval (95% CI). When the same measuring tools were adopted by clinical trials for measurement data, weighted mean difference (WMD) was calculated at 95% CI; otherwise, standard mean difference (SMD) was calculated at 95% CI. $P < 0.05$ was considered as statistically signifi-

**Table 1.** Characteristics of included studies in the meta-analysis

| Authors | Publication year | Study design | Random methods | Allocation concealment | Blind method | Baseline consistency | Dropout rate | Class |
|-------------|------------------|--------------|---------------------|------------------------|------------------|----------------------|--------------|-------|
| Alster | 1995 | QRCT | No description | No description | Double blind | Yes | 0% | B |
| Wittenberg | 1999 | QRCT | Random number table | Yes | Assessor-blinded | Yes | 5% | A |
| Manuskiatti | 2002 | QRCT | No description | No description | No description | Yes | 0% | B |
| Bowes | 2002 | QRCT | No description | No description | Assessor-blinded | Yes | 0% | B |
| Chan | 2004 | QRCT | No description | No description | No description | Yes | 0% | B |
| Omranifard | 2007 | QRCT | No description | No description | Assessor-blinded | Yes | 0% | B |
| Ni XL | 2013 | QRCT | No description | No description | No description | Yes | 0% | B |

cant. The existence of publication bias was checked using funnel plot if a sufficient amount of primary indicators were included.

Results

General features of included trials

Using the search strategies, 304 trials were identified in CCTR, MEDLINE Database, Embase, China Academic Journals Full-text Database and VIP database. After reviewing the titles and abstracts, 20 trials were selected, and 7 trials were finally included by reading the full text [11-17], the flow chart was shown in **Figure 1**. All trials were written in English or Chinese, and 268 scars (hypertrophic scars and keloids) in 259 subjects were included without limitation by age and gender. Among them, 7 trials divided one scar into different

parts to respectively receiving PDL and other therapies.

Efficacy determination

(1) Primary indicators: VSS was used to evaluate the size of erythema and scars (thickness, volume, length and width) along with blood flow, pliability and softness; (2) Secondary indicators: Secondary indicators were measured in all trials, including the symptoms and subjective evaluation of subjects; (3) Treatment time: All treatments lasted for 22 weeks to 2 years. The loss to follow-up rate was 5% in 1 trial [11] and 0% in the remaining trials; (4) Adverse reactions: Four trials reported adverse reactions, including intraoperative pain, purpura, pigmentation and blister [12-15]. One trial reported adverse reactions [13], and the remaining 2 trials reported no adverse reactions [11, 16].

Table 2. Meta-analysis of efficacy evaluation of 585 nm pulsed dye laser in pathological scars

| Indicator | Sample size | | Test of association | | | Test for heterogeneity | |
|------------------------------------|-------------|---------|---------------------|--------------|--------|------------------------|----------------|
| | Case | Control | WMD | 95% CI | P | P | I ² |
| VSS scores | 46 | 46 | -2.78 | -3.12, -2.46 | <0.001 | 0.51 | 0% |
| Erythema index | 16 | 16 | -5.30 | -8.08, -2.55 | <0.001 | - | - |
| Scar height | 16 | 16 | -2.30 | -3.40, -1.09 | <0.001 | - | - |
| Pliability rating of scars | 36 | 36 | -1.60 | -1.90, -1.09 | <0.001 | - | - |
| Self-assessment (>50% improvement) | 100 | 100 | 0.75 | 0.07, 2.25 | 0.004 | 0.44 | 0% |

Quality of the included trials

Of 7 randomized controlled trials (RCT), 1 trial performed computer-assisted creation of random number table for random allocation. Six QRCTs did not describe the method of random allocation. No allocation concealment was adopted except in 1 trial [12] (**Table 1**). One trial was double-blinded, and 3 trials were assessor-blinded; it was not certain whether blind method was used in 2 trials. All trials included follow-up procedures which lasted for 22 weeks to 2 years. The loss to follow-up rate was 0% in all except 1 trial where the loss to follow-up rate was 5%. It was not clarified in the latter whether intention-to-treat (ITT) analysis was performed.

Result analysis

Five trials compared the primary indicators and secondary indicators between 585 nm PDL group and non-treatment group. Two trials reported VSS scores and the results indicated a statistically significant decline of VSS scores compared with the control.

As shown in **Table 2**, mitigation of erythema was compared in 2 trials. One trial reported an obvious mitigation of erythema at week 32 after treatment. But no difference of statistical significance was found between 585 nm PDL group and the control group. The other trial indicated an obvious mitigation of erythema after 1 or 2 treatments, showing a statistically significant difference compared with the control. Different measuring methods were used in the 2 trials and the first trial did not report the original data, which made quantitative analysis impossible.

Height, length, width and volume of the scars were measured. Changes of the scar size were compared in 4 trials, and 3 of them described the height of the scars. One trial indicated a

marked decline of scars after 1 or 2 treatments compared with the control. Another trial reported an obvious decline of scar height at week 32 after treatment, showing statistically significant difference compared with the control ($P=0.005$), but no original data was included. One trial showed an insignificant decline of scar height between 585 nm PDL and blank control. The original data were incomplete in these 2 trials, therefore the data were not combined and analysis was carried out separately. One trial described the scar volume. Results of 40-week trial indicated no significant difference in scar volume between 585 nm PDL group and the blank control. As to pliability and hardness, 4 trials compared scar pliability and hardness and 2 trials described scar hardness. In 1 trial, scar hardness reduced considerably at the end of 1 ($P=0.0007$) or 2 treatments, showing a significant difference compared with the control. Another trial indicated a decline of scar hardness at week 32 after 585 nm PDL treatment compared with the baseline, but the difference was not significant ($P=0.02$); for the control group, a significant difference was noted at week 24 compared with the baseline ($P=0.046$), but this difference did not persist to week 32. Since this trial did not report the original data, it could not be combined with the above trials. Two trials described scar pliability; 1 trial reported no significant differences in pliability between the treatment group and the control group, but this trial did not report the original data. One trial involved the use of skin elasticity meter in the measurement of pliability, and a significant difference between the treatment group and the control group was observed only in 1 out of 5 measurements. The 2 trials were not combined due to the lack of original data.

Two trials reported patients' subjective evaluation. One trial indicated that the proportion of

585 nm and pathological scars

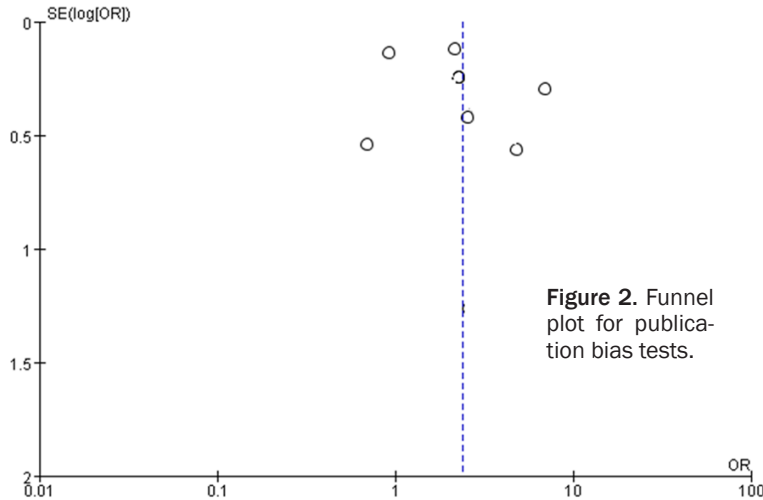


Figure 2. Funnel plot for publication bias tests.

patients reporting an improvement by 50% or above in self-evaluation did not differ significantly between the treatment group and blank control group. In another trial, the patients in treatment group reported an obvious improvement regarding itch, pain, sensitivity and scar size during subjective evaluation, and the difference was significant compared with the control. However, rate of obvious improvement subjectively evaluated by patients in terms of pinprick sensation and color change did not differ considerably between the two groups. The overall scores of the treatment group were much higher than those of the blank control.

One trial reported scores for itch and pain. According to this trial, 585 nm PDL and blank control did not differ significantly in their effects in improving the sensation of itch and pain.

Publication bias of the included literature

Funnel plot was used to test the publication bias of all included studies. Funnel plot shape of all included studies prompted no obvious asymmetry (**Figure 2**), suggesting no obvious publication bias.

Discussion

In the present study, we performed a meta-analysis to reveal efficacy and safety of 585 nm PDL in pathological scar and found 585 nm PDL is safe and effective in treating pathological scars.

Most of the seven trials included for systematic review were not sufficiently randomized. Random allocation was either implemented improv-

erly or not adopted at all. Allocation was concealed in only 1 trial. An accurate random allocation can avoid selection bias and reduce intergroup differences in RCT. The method for random allocation should be properly chosen and the allocation be fully concealed simultaneously. However, the included trials contained high selection bias with double-blind method adopted in only 1 trial and single-blind method in 3 trials. The remaining 3 trials did not clarify whether blind-method

was used. In that case, implementation bias and measurement bias were inevitable. Only 1 trial had a loss to follow-up rate of 5%, and that of the remaining trials was controlled within 10%. In spite of the biases, the included trials generally had a high quality.

VSS is an important measuring tool for pathological scars from the dimensions of scar size, texture and hardness. As shown by systematic review of the included trials in these dimensions, 585 nm PDL is generally effective for improving VSS scores. Moreover, 585 nm PDL also improved scar size and pliability and erythema, but no consistent and explicit conclusion regarding the efficacy of 585 nm PDL was reached in any of these dimensions. For pathological scars with poor improvement in height, erythema or pliability, other therapies should be adopted in combination. Patients' subjective evaluation indicated that 585 nm PDL has no overall efficacy or efficacy in improving the sensation of itch and pain. This technique is not the patient-preferred therapy.

Many studies have been carried out over 585 nm PDL. But meta-analysis is difficult because of the following problems: (1) The method for random allocation was not properly chosen for RCTs. Random number table was the most commonly used, or no description was provided for the selected random method at all; (2) Most studies contained no control groups but only treatment effect observation, leading to poor reliability of the conclusions; (3) Different scar evaluation indicator systems and measurement methods were adopted. Scar assessment scales also varied greatly from one trial to

another, and some were even designed by the researchers. This makes the evaluation of the efficacy difficult. We suggest the use of VSS or newly designed scales, and for patients' subjective evaluation, the Patient and Observer Scar Assessment Scale are recommended. The later covers the subjective evaluation by both patients and doctors. Some studies have demonstrated that this scale is more reliable than VSS; (4) Current studies are less concerned with the psychological impact of 585 nm PDL, improvement of patients' life quality or cost-benefit analysis; (5) Hypertrophic scars and keloids can be easily confused due to morphological similarities. Although the two types of scars show distinct clinical and physiological features, no subgroup analysis was included in most literature; (6) many studies only provide diagrams of the results but no original data.

In conclusion, 585 nm PDL is generally safe and effective for pathological scars. However, the findings need to be confirmed by more studies given the limited number of included trials.

Disclosure of conflict of interest

None.

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