Efficacy of photodynamic therapy in the treatment of actinic keratosis: a network meta-analysis

Yuanyuan Wan  
Central South University Third Xiangya Hospital

Qinghai Zeng  
Central South University Third Xiangya Hospital

Ling Jiang  
Central South University Third Xiangya Hospital

Chuhan Fu  
Central South University Third Xiangya Hospital

Shunmin Mao  
Central South University Third Xiangya Hospital

Lan Zhang  
Central South University Third Xiangya Hospital

Yushan Zhang  
Central South University Third Xiangya Hospital

Xiaolin Zhang  
Central South University Third Xiangya Hospital

Lu Zhu  
Central South University Third Xiangya Hospital

Fan Zhang  
Central South University Third Xiangya Hospital

Jing Chen  
Central South University Third Xiangya Hospital

Li Lei (✉ 676747867@qq.com  )  
Central South University Third Xiangya Hospital

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Abstract

**Background:** Photodynamic therapy (PDT) is a highly effective treatment for actinic keratosis (AK), and uses different light sources as well as photosensitizers. In addition, PDT is often combined with other physical therapies or drugs. A network meta-analysis (NMA) allows for comparison between treatments not directly compared in randomized controlled trials (RCTs). This study's objective was to compare the efficacy of different PDTs against AK lesions based on complete response rate (CR) by conducting a NMA.

**Methods:** The RCTs on the treatment of AK using PDT were screened, and a Bayesian model was developed using GeMTC 0.14.3 software to perform a NMA. The subgroups demarcated on the basis of the light sources and photosensitizers were also compared. RevMan 5.4.0 software was used to compare the outcome measure of different light sources in terms of relative risk ratio (RR) and a 95% confidence interval (CI). The therapeutic effects of different photosensitizers were compared using R 4.2.1 software and gemtc package version 1.0-1. The quality of the included literature was evaluated using the risk of bias assessment tool in RevMan 5.4.0, and the network plots between studies were drawn using STATA 16.0 software.

**Results:** Twenty-six trials involving 2285 patients and 14 treatments were included in the NMA. The results of the NMA showed that ablative fractional laser (AFL)-assisted methyl 5-aminolevulinic acid (MAL)-light-emitting diode (LED)-PDT had the best possible efficacy (Rank 1=0.56), followed by calcipotriol (CAL)-assisted MAL-LED-PDT (Rank 1=0.34) and 5-aminolaevulinic acid (ALA)-LED-PDT (Rank 1=0.05). The subgroup analysis showed that MAL-based PDT had better efficacy when using LED versus other light sources (RR 1.05 95% CI 1.03-1.07), and LED-based PDT resulted in the best possible efficacy when using ALA (Rank 1=0.47) versus other photosensitizers.

**Conclusions:** AFL combined with MAL-LED-PDT is most likely the best treatment option for AK. In case of monotherapies, PDT based on LED light source and ALA photosensitizer is a suitable choice.

Background

Actinic keratosis (AK), also known as senile keratosis or solar keratosis, is a chronic progressive precancerous lesion caused by prolonged exposure to ultraviolet light, and is characterized by rough erythema, plaques and scaly papules on the skin [1]. It often appears on sun-exposed areas, such as the face, scalp, neck and extremities. AK can progress to squamous cell carcinoma (SCC) [2]. Since it is difficult to predict whether AK will progress to SCC, early diagnosis and treatment is imperative [2].

Photodynamic therapy (PDT) involves the application of a photosensitizer to the affected site, which absorbs light at the appropriate wavelength and generates reactive oxygen species (ROS) to selectively destroy the diseased cells [3, 4]. It is a suitable topical treatment option for AK on account of its short intervention time, high efficiency and few side effects [3]. Effective PDT depends on an appropriate photosensitizer, light source and oxygen. The photosensitizers currently used for PDT are 5-
aminolevulinic acid (ALA) and methyl 5-aminolevulinate (MAL) [4]. A nanoemulsion of 5-aminolevulinic acid (BF-200 ALA) has also been tested as a photosensitizer [4]. The light sources commonly used for skin lesions include light-emitting diodes (LED), daylight (DL), pulsed dye laser (PDL), intense pulsed light (IPL), fabric-based biophotonic device (F) and visible light-water-filtered infrared A (VIS-wIRA) light [4–10]. The complete response rate (CR) of PDT for thin AK lesions is higher than that for medium and thick lesions [11]. In addition, the combination of physical (curettage, microdermabrasion, fractional ablative lasers, microneedling) or chemical (5-fluorouracil, calcipotriol, imiquimod) interventions with PDT can improve the penetration of photosensitizers and achieve better therapeutic results [12].

Although several studies have compared the efficacy of different light sources, photosensitizers and other treatment modalities in combination with PDT for AK [5–30], direct comparisons are lacking. Network meta-analysis (NMA) simultaneously compares the direct and indirect evidence from different studies, and thus expands the scope of conventional meta-analysis by estimating the relative efficacy of all interventions and ranking them even in the absence of direct comparison between any two interventions [31]. No systematic review so far has pooled the effects of different PDT treatments for AK lesions based on the outcomes of CR. Therefore, the aim of this study was to conduct an NMA of the randomized controlled trials (RCTs) and compare the relative efficacy of different PDT strategies against AK lesions based on complete CR.

Methods

Study selection

PubMed, Embase, Web of science, Cochrane clinical trials database and Wiley online library databases were searched for RCTs published till September 2022 that analyzed the effect of PDT on AK lesions. The articles were searched using the following key words: "Keratosis, Actinic", "Photodynamic therapy", "Randomized controlled trial". Only RCTs conducted on human subjects were included. Endnote 20 was used to manage the literature search records. Two authors independently examined the titles, abstracts and keywords of the screened literature, and selected the qualified articles for full-text review by a third researcher. The inclusion criteria for the studies were as follows: 1) RCT design, 2) non-immunocompromised adult subjects with clinically or pathologically confirmed primary AK of the face, neck or extremities, 3) at least one group treated with mono-PDT or combination therapy (dose studies or trials with unconventional treatment doses or schedules were excluded, and small differences in treatment doses or schedules were considered equivalent), and 4) outcome measure was the complete response (CR) rate (i.e. the number of completely treated lesions in each area divided by the total number of lesions treated) 3 months after the first treatment (studies that reported complete clearance rate of patients, number of lesion clearance or lesion response rate were excluded).

Data extraction and outcome measures

Two authors independently read the full text of the included articles and extracted the relevant data. Any disagreements were resolved by discussion between reviewers and consultation with a third researcher.
The following data were extracted: first author, year of publication, treatments, number of patients (number of lesions), average age of patients (mean ± SD), male to female ratio, Olsen score, and Fitzpatrick skin type. The primary outcome measure was the CR at 3 months after the first treatment. For studies with multiple courses of treatment, including MAL-PDT and BF-200 ALA-PDT, the CR 3 months after the first course of treatment was considered.

**Intervention categories**

The studies in this NMA included a total of 14 treatments. The monotherapies were 1) MAL-DL-PDT, 2) MAL-LED-PDT, 3) MAL-F-PDT, 4) MAL-IPL-PDT, 5) MAL-PDL-PDT, 6) ALA-LED-PDT, 7) ALA-VIS-wIRA-PDT, 8) BF-200 ALA-LED-PDT, 9) BF-200 ALA-DL-PDT, 10) placebo (Pla)-LED-PDT, and 11) Pla-IPL-PDT. The combination therapies included 1) 5-fluorouracil (5-Fu)-assisted MAL-DL-PDT, 2) calcipotriol (CAL)-assisted MAL-LED-PDT, and 3) ablative fractional laser (AFL)-assisted MAL-LED-PDT.

**Risk-of-bias assessment**

The risk of bias associated with the different interventions was summarized using the bias risk assessment tool in RevMan 5.4.0. The following domains were considered: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data, (vi) selective reporting, and (vii) other bias. Each intervention was classified as "high risk", "low risk" or "unclear risk".

**Network meta-analysis**

NMA was performed using GeMTC 0.14.3 software, a Bayesian generalized linear model using a consistency model. Four chains with 20,000 iterations and a burnin of 50,000 iterations were run. The outcome measure of the NMA was CR 3 months after the first treatment. The estimated treatment effect size and associated uncertainty were translated into the probability that a certain treatment was the most effective [2]. The ‘networkplot’ function of STATA 16.0 was used to create network plots that describe the geometry of the different interventions. The nodes represent the number of participants in that intervention type, and the thickness of lines between interventions indicate the number of studies for that comparison [32].

**Subgroup analysis**

Subgroup analyses were performed based on different light sources and photosensitizers, and the outcome measure was CR 3 months after the first treatment. RevMan 5.4.0 was used to compare the outcome measures of PDT based on different light sources. The measure of effect for each outcome was presented as relative risk ratio (RR) with a 95% confidence interval (CI). RR ≠ 1 indicated that the test factor has an impact on the disease, and smaller the RR value, the better the test factor works on the disease. The heterogeneity across studies was tested using the I2 statistic [33], and the fixed effect model was used for the pooled data. This network meta-analysis was performed using R 4.2.1 software and gemtc package version 1.0-1 to compare the outcome measure of PDT treatments based on different
photosensitizers. Ranks the treatments based on their likelihood of having the desired effect on the outcome being measured.

Results

Study inclusion

A total of 1356 articles were retrieved in the initial search, of which 579 remained following removal of duplicate publications. Another 402 articles were excluded after screening the titles and abstracts, followed by 151 articles based on the full text. Finally, 26 RCTs that met the inclusion criteria were included in the NMA. The study selection flowchart is shown in Figure 1.

Study characteristics, quality and bias assessment

The 26 RCTs included a total of 2285 patients, who were followed up for no more than 1 year after treatment. Five studies compared MAL-DL-PDT and MAL-LED-PDT [13-17], one study compared MAL-DL-PDT and 5-Fu-MAL-DL-PDT [18], and one study compared CAL-MAL-LED-PDT and MAL-LED-PDT [12]. In addition, AFL-MAL-LED-PDT and MAL-LED-PDT were compared in 4 studies [11,19-21], ALA-LED-PDT and Pla-LED-PDT in 2 studies [22,23], MAL-DL-PDT and Pla-LED-PDT in 2 studies [24,25], BF-200 ALA-LED-PDT and Pla-LED-PDT in 2 studies [26,27], BF-200 ALA-LED-PDT, MAL-LED-PDT and Pla-LED-PDT in one study [28], BF-200 ALA-DL-PDT and MAL-DL-PDT in 2 studies [29,30], and MAL-LED-PDT and MAL-F-PDT in 2 studies [5,6]. One study each compared MAL-IPL-PDT and Pla-IPL-PDT [7], MAL-IPL-PDT and MAL-LED-PDT [8], MAL-PDL-PDT and MAL-LED-PDT [9], and ALA-VIS-wlRA-PDT and ALA-LED-PDT [10]. The detailed characteristics of these studies are summarized (show in Table 1). The primary cause of bias was the inability to blind the participants to certain phototherapy protocols, such as those using sunlight as the light source, and only 8 studies were conducted in a double-blinded manner for researchers and participants [7,11,17,24-26,28,30]. The secondary causes of bias were the loss of patients during follow-up [10,14,28] and the selective reporting [14,19,21]. Furthermore, 3 studies did not describe the method of randomization [9,22,23] and 12 studies did not clearly demonstrate that the allocation concealment was adequate [9,10,12,20-24,26,27,29,30], resulting in selection bias. The risk of bias in the included studies are summarized (Fig. 2)

Treatment network

The NMA map of the 26 studies is shown in Figure 3. Most studies had MAL-LED-PDT as a conventional treatment, which corresponded to the highest number of patients (n = 896), followed by MAL-DL-PDT (n = 387) and Pla-LED-PDT (n = 420). Furthermore, the comparison between MAL-LED-PDT and MAL-DL-PDT was most frequent, with a total of 5 studies including 301 patients and 7205 lesions. MAL-LED-PDT and AFL-MAL-LED-PDT were compared in 4 studies, and included 189 patients and 944 lesions.

Network meta-analysis results
NMA was performed using GeMTC 0.14.3 software, and the possible efficacy of the different treatments were ranked (Fig. 4). As shown in Table 2, AFL-MAL-LED-PDT had the highest likelihood of achieving CR through both direct and indirect comparison (P = 0.56), followed by CAL-MAL-LED-PDT (P = 0.34) and ALA-LED-PDT (P = 0.05). The complete matrix of results is shown in Additional file 1. In addition, the direct comparison between the PDT intervention types reported in the original trials is summarized (Additional file 2).

Subgroup analysis

Subgroup analysis was performed to compare the effects of different light sources and photosensitizers on the efficacy of PDT. Since most studies used MAL as the photosensitizer, the efficacy of different light sources was compared using MAL-based PDT studies. Nine RCTs compared the 3-month CR of MAL-based PDT using 6 different light sources (LED, DL, F, IPL, PDL and VIS-wIRA), with LED as the control [5,6,8,9,13-17]. We divided these studies into the MAL-LED-PDT group (4665 lesions) and the different MAL-non-LED-PDT groups (4689 lesions) for pairwise comparisons. As shown in the forest plots (Fig. 5), PDT using LED as the light source had a statistically higher CR compared to monotherapies using other light sources (RR: 1.05, 95% CI: 1.03-1.07). Furthermore, the probability of good to complete response of the AK lesions was significantly higher with MAL-LED-PDT compared to MAL-DL-PDT (RR: 1.05, 95% CI: 1.03-1.08), whereas no significant differences were observed when MAL-LED-PDT was compared to MAL-F-PDT (RR: 0.98, 95% CI: 0.91-1.06), MAL-IPL-PDT (RR: 1.22, 95% CI: 0.95-1.56) or MAL-PDL-PDT (RR: 1.06, 95% CI: 0.96-1.17). Thus, the curative effect of PDT using F, IPL and PDL as the light source is similar to that using LED as the light source. Since only one study has compared VIS-wIRA as a light source with ALA-LED-PDT, it was not included in the subgroup analysis [10].

Seven studies including 1415 participants and 4 different photosensitizers (ALA, MAL, BF-200 ALA, Pla) were used for the subgroup analysis of different photosensitizers based on LED light sources [22-28]. Due to the lack of direct comparison between MAL-LED-PDT and ALA-LED-PDT, MAL-LED-PDT could not be used as a control. NMA analysis was performed using R 4.2.1 software and gemtc package version 1.0-1. The ranking of the PDT interventions using different photosensitizers based on their likelihood of effecting CR is shown in Figure 6. ALA was associated with the highest probability of CR (P = 0.47), followed by BF-200 ALA (P = 0.40) and MAL (P = 0.13) (show in Table 3).

Discussion

NMA was performed on 26 studies with a total of 2285 patients that compared the efficacy of different photodynamic monotherapies (MAL-DL-PDT, MAL-LED-PDT, ALA-LED-PDT, Pla-LED-PDT, BF-200 ALA-DL-PDT, BF-200 ALA-LED-PDT, MAL-F-PDT, ALA-VIS-wIRA-PDT, MAL-IPL-PDT, Pla-IPL-PDT, MAL-PDL-PDT) and combination therapies (5-Fu-MAL-DL-PDT, CAL-MAL-LED-PDT, AFL-MAL-LED-PDT) against AK lesions. Based on our results, AFL-MAL-LED-PDT may have the best curative effect in terms of the CR 3 months after the first treatment. Followed by CAL-MAL-LED-PDT had the better efficacy, while ALA-LED-PDT was the most effective monotherapy. Although PDT is a widely approved therapy for AK [34], the
monotherapy results in slightly lower clearance rate of AK lesions with hyperkeratosis [11]. Therefore, PDT is often combined with other physical and chemical therapies to improve its therapeutic efficacy, especially against Olsen grade II-III AK lesions [21]. The results of our NMA also suggested that PDT combined with AFL and CAL is more effective than PDT alone, which is consistent with the conclusions of other studies [11,12,19-21]. The high curative effect of AFL-MAL-LED-PDT can be attributed to the AFL. Four studies analyzed the effects of AFL-MAL-LED-PDT against AK [11,19-21], of which 2 studies used ablative fractional CO2 laser [11,20] and 2 studies used Er:YAG laser [19,21]. AFL surface pretreatment increases porphyrin synthesis and photodynamic activation by removing surface warts, creating microscopic vertical channels, and promoting the penetration and absorption of topically applied photosensitizers [11,21]. Therefore, AFL can increase the bioavailability of photosensitizers in the skin and enhance therapeutic response [11,21]. The exact mechanism of CAL-assisted PDT is unclear. Studies show that CAL pretreatment may increase cell lysis, photosensitizer absorption and the accumulation of protoporphyrin IX (PpIX) in the skin, and therefore augment the effects of PDT [12]. On the other hand, the efficacy of 5-Fu-MAL-DL-PDT was low, most likely due to the limited number of studies. Therefore, further investigation is needed to ascertain the efficacy of this combination therapy. Furthermore, only limited data was available on other therapies used in combination with PDT, such as curettage, microdermabrasion, microneedling, imiquimod et al, and were thus not included in the NMA.

Since the light source and photosensitizer significantly affect the overall efficacy of PDT [4], we conducted subgroup analyses based on the two variables. PDT using LED had overall better efficacy compared to regimens using other light sources, although statistical significance was only observed for the comparison between MAL-LED-PDT and MAL-DL-PDT, while MAL-F-PDT, MAL-IPL-PDT and MAL-PDL-PDT were similarly effective as MAL-LED-PDT. Nevertheless, the high therapeutic efficacy of AFL-MAL-LED-PDT and CAL-MAL-LED-PDT can also be attributed to the use of LED as light source. Contradictory to our findings however, some studies have reported similar curative effect of LED-PDT and DL-PDT [13-17]. DL-PDT has several advantages, such as good tolerance, almost no pain, greater convenience, fewer serious adverse events and high patient satisfaction, and can be considered as the first choice for patients with mild to moderate AK [13-17]. Furthermore, subgroup analysis of the photosensitizers showed that ALA was associated with the best curative effect, followed by BF-200ALA and MAL. Addition of methyl groups to ALA generates MAL, which is more lipophilic and has a higher penetrative power, resulting in greater therapeutic effect [24,25]. However, our results indicate that ALA has a better therapeutic effect than MAL, whereas other studies have reported similar therapeutic effects of MAL-PDT and ALA-PDT [3]. Therefore, further research is needed to clarify this point. BF-200ALA is a nanoemulsion of ALA with enhanced stability and skin penetration, and has shown higher AK lesion clearance compared to ALA [3]. However, we found that the curative effect of ALA was better than that of BF-200ALA, and will have to verify this result with subsequent studies. Based on the subgroup analysis, switching MAL with ALA or BF-200ALA may improve the lesion clearance rate of AFL-LED-PDT, and warrants further investigation.

The results of this NMA provide a theoretical basis for selecting the optimum PDT regimen for AK. However, there are certain limitations in this NMA in the context of clinical practice and decision-making.
First, the number and quality of the studies included in the NMA were not sufficient. Furthermore, some treatments were not included in the NMA since their measures of outcome did not meet the inclusion criteria of this NMA. Second, some treatment regimens such as MAL-PDT and BF-200 ALA-PDT are repeatedly administered, although we only included in the CR 3 months after the first course of treatment in our analysis. Finally, only a limited number of studies had long-term follow-up of patient, and the recurrence of cleared lesions could not be analyzed. We also did not consider differences in adverse events, cosmetic outcomes, patient satisfaction, treatment cost and so on. However, the data regarding the relative efficacy of different PDT regimens against AK may provide a reference for future clinical applications.

**Conclusions**

AFL-MAL-LED-PDT is most likely to achieve complete clearance of AK lesions, and PDT using LED as the light source and ALA as the photosensitizer maybe more effective for the treatment of AK. However, more RCTs are needed to verify the results of this analysis.

**Abbreviations**

PDT Photodynamic therapy

AK Actinic keratosis

NMA Network meta-analysis

CR Response Rate

RCT Randomized Controlled Trials

RR Relative Risk Ratio

CI Confidence Interval

MAL Methyl 5-aminolevulinic acid

DL Daylight

LED Light-emitting diode

F Fabric-based biophotonic device

IPL Intense pulsed light

PDL Pulsed dye laser

ALA 5-aminolaevulinic acid
VIS-wIRA visible light - water-filtered infrared A
BF-200ALA 5-aminolevulinic acid nanoemulsion
Pla Placebo
5-Fu 5-fluorouracil
CAL Calcipotriol
AFL Ablative fractional laser
SCC Squamous cell carcinoma
ROS Reactive oxygen species

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests
The authors declare that they have no competing interests

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Authors' contributions
LL: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Visualization, Funding acquisition. YW: Investigation, Resources, Writing original draft, and was a major contributor in writing the manuscript. QZ: Writing – review & editing. LJ: Investigation, Resources, Validation, Writing – review & editing. CF: Investigation, Resources, Validation. SM: Investigation,
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Not applicable

References


Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures
Figure 1

Flow-chart of study selection.
Figure 2

Risk-of-bias analysis. A. Risk of bias summary, a summary table of review authors' judgements for each risk of bias item for each study; B. Risk of bias graph, a plot of the distribution of review authors' judgements across studies for each risk of bias item.
Figure 3

Network meta-analysis maps of the studies examining the efficacy of photodynamic treatments for actinic keratosis.
Figure 4

Ranking plots for the CR of the comparison among different PDT treatments of AK.
Figure 5

Forest plot for the effect of comparing MAL-LED-PDT with MAL-Non-LED-PDT.
Figure 6

Ranking plots for the CR of the comparison among PDT treatments using different photosensitizers.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.doc
- Additionalfile2.pdf
- table1.xls
- table2.xls
- table3.xls