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Review

Daylight versus conventional photodynamic therapy for the treatment of actinic keratosis: A meta-analysis of randomized controlled trials

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ABSTRACT

Daylight photodynamic therapy (dPDT) is suggested to be effective for actinic keratosis (AK). We performed a meta-analysis of randomized controlled trials (RCTs) to compare the efficacy and safety of dPDT versus conventional photodynamic therapy (cPDT) in patients with AK. Relevant studies were identified through a systematic search of PubMed, Embase, and the Cochrane Library. A fixed or random effect model was applied, depending on the heterogeneity. Six RCTs with 369 patients with 5,556 AK lesions that were undergoing dPDT or cPDT with red light and methyl aminolevulinate (MAL) were included. Overall, the incidence of complete response (CR) was not significantly different between the two groups (risk ratio [RR]: 0.93, $p = 0.07$). Subgroup analyses indicated that dPDT was non-inferior to cPDT for CR in studies only included grade I–II AK lesions (RR: 0.97, $p = 0.41$), but less effective for CR in studies which also included grade III lesions (RR = 0.87, $p < 0.001$). Subsequent meta-analyses showed that dPDT was associated with a significantly reduced maximal pain score (mean difference = -4.51, $p < 0.001$) and a lower risk of adverse events (RR = 0.70, $p < 0.001$) as compared with cPDT. These results suggested although dPDT was better tolerated, the treatment efficacy of dPDT is non-inferior to cPDT with red light and MAL only in grade I–II AK lesions. The relative therapeutic efficacy of dPDT in AK of grade III lesions in comparison with cPDT should be further evaluated.

1. Introduction

Actinic keratosis (AK) is a common skin lesion that is found in Caucasian people. The reported prevalence of AK is up to 50% in males and 30% in females from European countries [1,2]. It has been confirmed that during the progression of the disease, some patients with AKs develop invasive squamous cell carcinoma (SCC) due to the malignant transformation of AK [3]. Previous studies showed that the average one-year transformation rates per one AK lesion were 0.075%～0.096% [4], and the 10-year neoplastic transformation rates of an average affected patient with 7.7 A K lesions varied from 10.2% to 20.0% [5].

Accumulating evidence from clinical trials indicates that photodynamic therapy (PDT) has become an important treatment strategy for AK [6–8]. During conventional PDT (cPDT), a photosensitizer is activated following red-light or blue-light exposure, and subsequently the activated oxygen species are produced to destroy the targeted cells and tissues [9,10]. Although it has been indicated that topical cPDT is effective for patients with AK, particularly for those with large size and multiple lesions, the clinical application of this treatment strategy can be limited by the associated pain and topical adverse events that are linked to the treatment [11]. Interestingly, recent studies have suggested that daylight PDT (dPDT) may also exert similar therapeutic efficacy in patients with AK without the incidence of significant pain or other related topical adverse events to the skin lesion [12]. Indeed, several pilot randomized controlled trials (RCTs) have indicated that the therapeutic efficacy of dPDT is non-inferior to cPDT in AK [13–18]. Moreover, dPDT could be well tolerated by patients with AK because it is nearly painless and leads to few related adverse events to the skins [19]. However, these RCTs were all of limited sizes, and, to the best of our knowledge, an overall comparison of the efficacy and safety of dPDT and cPDT has not been evaluated in a meta-analysis previously. Therefore, in this study, we aimed to compare the treatment efficacy and safety of dPDT and cPDT in patients with AK by combining the results of previously published RCTs. Moreover, we also explored whether the characteristics of AK lesions could affect the treatment efficacy of dPDT versus cPDT.

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2. Methods

This systematic review and meta-analysis was designed and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20] and the Cochrane Handbook guidelines [21].

2.1. Search strategy

PubMed, Embase and the Cochrane Library (Cochrane Center Register of Controlled Trials) databases were systematically searched for relevant studies, using the search terms "solar keratosis" or "actinic keratosis", combined with "photodynamic therapy", "photochemotherapy", and "random", "randomly", or "randomized". The search was limited to studies in humans. We also manually analyzed the reference lists of the original and review articles. The final database search was performed on June 15th, 2018.

2.2. Study selection

Studies were included if they met the following criteria: 1) published as full-length articles in English; 2) reported as RCTs with a parallel design; 3) included patients with clinically or histologically diagnosed AK who were assigned to either a dPDT treatment group or a cPDT treatment group (regardless of the lights and sensitizers used and regimens of either treatment); 4) reported at least one of the following outcomes: efficacy as reflected by the incidence of complete response (CR) of AK, tolerance as indicated by the maximal pain score, and safety as demonstrated by the incidence of severe adverse events (AEs). No restriction was applied to the follow-up durations of RCTs. Reviews, nonhuman studies, observational studies, duplicate publications, and studies in which the outcomes of interest were not reported or unavailable were excluded from the meta-analysis.

2.3. Data extraction and quality assessment

Two authors performed the literature search, data extraction, and quality assessment independently, in accordance with the inclusion criteria. Discrepancies were resolved by consensus. Extracted data included the location of the study, study design characteristics (blind or open-label, intra-individual study or not), patients and lesion characteristics (number of participants, mean age, gender, and grade and distribution of the AK lesions), treatment regimen (sensitizer, session, incubation time and light source in each group), and follow-up durations. We applied the seven domains of the Cochrane's Risk of Bias Tool to evaluate the quality of the included studies [21], which includes criteria regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity.

2.4. Statistical analysis

Dichotomous data were analyzed using risk ratios (RRs) with 95% confidence intervals (CIs), while continuous data were presented as mean difference (MD) with 95% CI. Cochrane's Q test was applied to evaluate the heterogeneity among the included studies, and significant heterogeneity was considered to be $P < 0.10$ [22]. The I^2 statistic, which describes the percentage of the total variation across studies that is due to heterogeneity rather than to chance [22], was also calculated. An $I^2 > 50\%$ indicated significant heterogeneity. Pooled analyses were calculated using fixed-effect models if no significant heterogeneity was detected by Cochrane's Q test, whereas random-effect models were applied if significant heterogeneity was found [21]. Predefined subgroup analyses were used to evaluate whether the incidence of CR of the AK lesions was affected by the degree of lesions, or the follow-up duration [23]. Potential publication bias was evaluated using the Egger's regression asymmetry test [24] and visual inspection of funnel plots. P values were two-tailed and statistical significance was set at $p \leq 0.05$. RevMan (Version 5.1; Cochrane, Oxford, UK) and Stata software (Version 12.0; Stata, College Station, TX) were used to perform the statistical analysis.

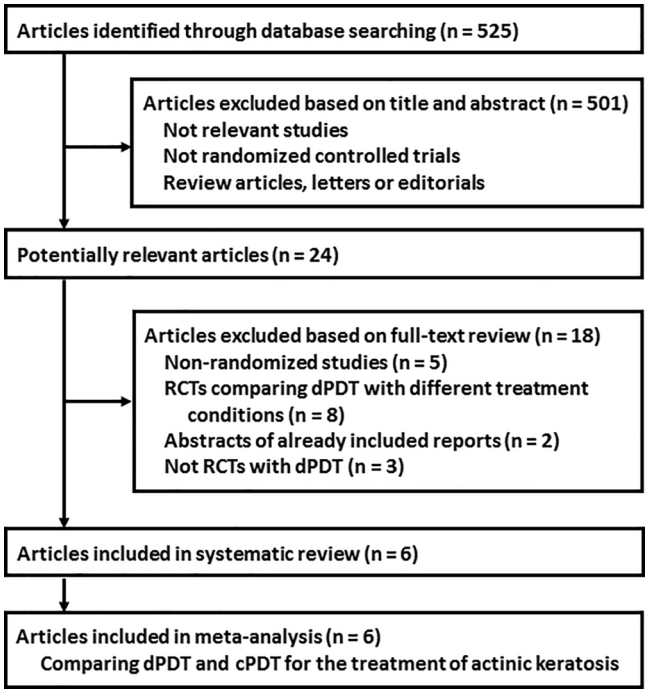

Fig. 1. Flowchart of the literature search.

3. Results

3.1. Search results

A total of 525 articles were identified through the database searches. Five-hundred and one of these articles were excluded through title and abstract screening, mainly because they were not relevant to the purpose of this study. Of the 24 potentially relevant articles, six studies met the inclusion criteria for the current meta-analysis [13–18] (Fig. 1). Eighteen articles were excluded for the following reasons: five of them were not randomized studies, eight were RCTs that compared dPDT with different treatment conditions, two were abstracts of already included RCTs, and the two did not include an arm of dPDT treatment.

3.2. Study characteristics

Overall, six RCTs of 369 patients with AK were included [13–18]. The characteristics of the included RCTs are summarized in Table 1. These studies were performed in Europe or Australia, and five of them were intra-individual studies (13–1618)). Old patients with AK (mean ages: 63–78 years) were included, and one study included organ transplant recipients with AK [16]. For all of the studies, methyl aminolevulinate (MAL) was used as the sensitizer for PDT. For patients allocated to the dPDT group, daylight illumination for 2 h or 2.5 h was applied after the application of MAL for up to 0.5 h. For patients in the cPDT group, conventional red light illumination was performed after 3-h incubation with MAL. A single session of treatment was applied in five of the studies [13–16,18], while in one study, one session was applied in the case of grade I lesions and two sessions were applied in the case of grades II–III lesions [17]. The follow-up durations varied from three to 12 months.

Table 1
Characteristics of the included studies.

Study	Location	Design	Intra-individual study	Patients and lesion characteristics	Sample size	Age	Male	Sensitizer	Treatment session	d-PDT method	c-PDT light source and method	Follow-up duration
						years	%					months
Wiegell 2008	Denmark	R, SB	Y	AK of the face and scalp (grade I-III)	29	78.0	79.3	MAL	1 session	Daylight illumination for 2.5 h after MAL occlusion for 0.5 h	Red LED of 575–670 nm illumination after 3 h incubation with MAL	3
Rubel 2014	Australia	R, SB	Y	AK of the face and scalp (grade I-II)	100	66.9	75.0	MAL	1 session	Daylight illumination for 2 h after MAL occlusion for 0.5 h	Red light illumination after 3 h incubation with MAL	6
Togsverd-Bo 2015	Denmark	R, SB	Y	OTRs with AK of the scalp, chest and extremities (grade I-III)	16	63.0	62.5	MAL	1 session	Daylight illumination for 2 h after MAL application for 0.5 h	Red light of 630 nm illumination after 3 h incubation with MAL	3
Lacour 2015	Sweden, Germany, the Netherlands, France and Spain	R, SB	Y	AK of the face and scalp (grade I-II)	108	73.0	91.7	MAL	1 session	Daylight illumination for 2 h within 0.5 h after MAL application	Red light illumination after 3 h incubation with MAL	3
Neittaanmäki-Perttu 2016	Finland	R, OL	N	AK of the face or scalp (grade I-III)	70	76.0	55.7	MAL	1 session for grade I lesions and 2 sessions for grades II–III lesions	Daylight illumination for 2 h after MAL application for 0.5 h	Red light of 632 illumination after 3 h incubation with MAL	6
Sotiriou 2018	Greece	R, SB	Y	AK of the face or scalp (grade I-II)	46	73.6	66.7	MAL	1 session	Daylight illumination for 2 h after MAL application for 0.5 h	Red LED of 630 nm illumination after 3 h incubation with MAL	12

R, randomized; SB, single-blind; OL, open label; Y, yes; N, no; AK, actinic keratosis; MAL, methyl aminolevulinate; PDT, photodynamic therapy; LED light-emitting diode; OTRs, organ transplant recipients.

3.3. Data quality

The details of the risks of biases of the included studies according to the Cochrane assessment tool are listed in Table 2. Briefly, most of the included RCTs were single-blind [13–16,18] except for one study, which was open label [17]. The details of random sequence generation were reported in five studies [14–18]. The details of withdrawals and dropouts were reported in all studies.

3.4. Efficacy of dPDT versus cPDT for CR of AK lesions

All of the included RCTs reported the efficacy outcome of the CR of AK lesions. Pooled results of 5556 AK lesions showed that the CR was not significantly different between AK lesions that were allocated to the dPDT and cPDT groups (RR: 0.93, 95% CI: 0.86–1.01, p = 0.07; Fig. 2) with considerable heterogeneity (I^2 = 85%). Excluding the study [17] which was open label and not intra-individually designed did not significantly affect the results (RR: 0.95, 95% CI: 0.89–1.02, p = 0.19; I^2 = 80%). Subgroup analyses indicated that the CR was not significantly different between the AK lesions that were allocated to the dPDT and cPDT groups in studies where only grade I—II AK lesions were included (RR: 0.97, 95% CI: 0.91–1.04, p = 0.41; I^2 = 78%; Fig. 3A). However, for studies that included grade I-III AK lesions, the incidence of CR was significantly lower in the dPDT group than in the cPDT group (RR: 0.87, 95% CI: 0.81 to 0.94, p < 0.001; I^2 = 0). These results suggest that the grade of the AK lesions may affect the CR of the AK lesions to dPDT (p for subgroup difference = 0.03; Fig. 3A). Subsequent subgroup analyses showed that a difference in follow-up duration did not significantly affect the comparative efficacy of dPDT versus cPDT on the CR of AK lesions (p for subgroup difference = 0.96; Fig. 3B).

3.5. Influence of dPDT versus cPDT on maximal pain score in patients with AK

The pooled results of six RCTs showed that dPDT was associated with a significantly lower maximal pain score than the observed in the cPDT group (MD = -4.51, 95% CI: -5.12 to -3.89, p < 0.001; Fig. 4A), suggesting a better tolerance of the patients to dPDT as compared with that of cPDT.

3.6. Risks of AEs in patients with AK receiving dPDT versus cPDT

The risk of AEs were reported in all of the RCTs that were included in this study, while two studies defined serious AEs similarly, including erythema, scab, skin burning sensation, and skin edema [14,15]. The combined result showed that the incidence of AEs was significantly lower in the patients that received dPDT than in those that received cPDT (RR: 0.70, 95% CI: 0.58 to 0.85, p < 0.001; I^2 = 0; Fig. 4B).

3.7. Publication bias

The publication bias for the current meta-analysis was difficult to estimate because only six studies were included. On visual inspection, the funnel plots seemed to be symmetrical for both the meta-analyses comparing the CR of AK lesions and the influence on maximal pain score after dPDT or cPDT treatment (Fig. 5A and B). These findings were consistent with the results of the Egger's regression tests, which suggested no significant publication bias for the above meta-analyses (p = 0.32 and 0.88, respectively).

4. Discussion

In this meta-analysis, by pooling the all of the available data from RCTs, we found that the current evidence suggests that the overall therapeutic efficacies between dPDT and cPDT with red light and MAL are comparable for patients with AK, as reflected by an insignificant

Table 2
Quality evaluation of the included studies via the Cochrane's Risk of Bias Tool.

	Random sequence generation	Allocation concealment	Blinding in performance	Blinding in outcome detection	Incomplete outcome data	Reporting bias	Other bias
Wiegell 2008	High	Low	High	Low	Low	Unclear	Low
Rubel 2014	Low	Low	Low	Low	Low	Unclear	Low
Togsverd-Bo 2015	Low	Low	Low	Low	Low	Unclear	Low
Lacour 2015	Low	Low	Low	Low	Low	Unclear	Low
Neittaanmäki-Perttu 2016	Low	Low	High	High	Unclear	Unclear	Unclear
Sotiriou 2018	Low	Unclear	Low	Low	Low	Unclear	Low

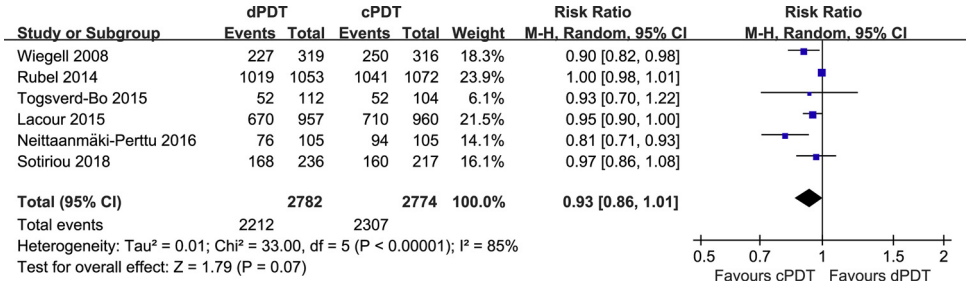

Fig. 2. Forest plots comparing the efficacy of daylight photodynamic therapy (dPDT) and conventional photodynamic therapy (cPDT) on the complete response (CR) of the actinic keratosis (AK) lesions.

change in the CR of AK lesions that were treated with dPDT and cPDT within a follow-up duration of up to 12 months. However, patients with AK that received dPDT were associated with a significantly lower maximal pain score and fewer incidence of AEs than in those that received cPDT with red light and MAL, indicating that dPDT is better tolerated than cPDT in patients with AK. Interestingly, the results of our subgroup analyses, according to the grade of AK lesions, suggest that dPDT was non-inferior to cPDT for the CR in the studies that only included grade I—II AK lesions. However, dPDT was found to be less effective than cPDT for the CR in studies that also included grade III lesions of AK, indicating that the grades of AK lesions may affect the relative therapeutic efficacy of dPDT and cPDT. Taken together, these results suggest that, although dPDT is better tolerated, the treatment efficacy of dPDT is non-inferior to cPDT with red light and MAL in grade I—II AK lesions only. The relative therapeutic efficacy of dPDT in patients with AK with grade III lesions in comparison with the therapeutic efficacy of cPDT with red light and MAL should be further evaluated.

The results of our study have several clinical implications. Firstly, the results of our study confirm the findings from previous pilot RCTs, that the overall therapeutic efficacy of dPDT is non-inferior to cPDT for AK, with a combined RR for the incidence of CR of 0.97. Moreover, evaluating the safety outcomes, we confirmed that dPDT is better tolerated than cPDT, since patients with AK that are treated with topical dPDT report significantly lower maximal pain scores and show fewer incidences of AEs to the skins than those that received cPDT. Based on the above findings, together with the convenience of dPDT, in that it does not require time consuming clinical visits, dPDT should be recommended for patients with AK. Furthermore, a recent trial from Finland indicated that dPDT is more cost-effective than cPDT for the treatment of AK, which is an additional reason to recommend dPDT. Secondly, subgroup analyses of our study, according to the follow-up duration, showed that differences in the follow-up duration did not significantly affect the comparative therapeutic efficacy of dPDT and cPDT on AK lesions, suggesting that the therapeutic efficacy of dPDT is stably non-inferior to cPDT during the follow-up duration of up to one year. Interestingly, the results of our subgroup analyses, based on the grades of AK that were included in each study, found that dPDT was non-inferior to cPDT for the CR in studies that only included grade I—II AK lesions. However, dPDT produced a less effective CR than cPDT in studies which also included grade III lesions of AK, suggesting that the current notion that dPDT is non-inferior to cPDT for the treatment of AK is mainly driven by studies that include grade I—II AK lesions. Moreover, the relative therapeutic efficacy of dPDT in comparison with cPDT in patients with AK of grade III lesions remains undetermined in the current stage. Based on the results of our subgroup analyses, we speculated that dPDT may be less effective than cPDT in the treatment of grade III AK lesions [25]. It has been indicated in a previous study that the CR of patients with AK that received dPDT decreased gradually as the severity of the AK lesions increased (grade I-III) [26]. To the best of our knowledge, the relative therapeutic efficacy of dPDT and cPDT has not been directly compared in grade III AK lesions. Obviously, further RCTs are needed to confirm our hypothesis. Finally, our results highlight the importance of further optimization of the regimens of dPDT for patients with AK, particularly for the treatment of grade III AK lesions. Theoretically, increasing the number of sessions of dPDT, using sensitizers of higher concentrations of MAL, increasing the daylight exposure time and pretreatment of AK lesions before dPDT may all potentially improve the therapeutic efficacy of dPDT [27–29]. Whether these strategies could strengthen the therapeutic efficacy of dPDT for grade III AK requires further investigations.

There are some limitations of this study which should be considered when interpreting the results. Firstly, significant heterogeneity existed regarding the meta-analysis of the CR of AK. Although we applied subgroup analyses to explore the source of the heterogeneity and found that the different grades of AK may contribute to the heterogeneity among the included studies, we could not exclude other sources of heterogeneity, such as differences in the conditions of daylight exposure (intensity and temperature etc.), and the experience of the therapists and study centers. Secondly, because limited RCTs were included and we did not have access to the individual patient data, the results of subgroup analyses were performed based on the data at the study level. The exact influence of study characteristics, such as the grade of AK lesions, on the relative efficacy of dPDT and cPDT should be directly investigated and compared in RCTs. Moreover, the qualities of the included RCTs were moderate, which may thereby bias the results. However, sensitive analyses through the exclusion of the open label trial did not significantly change the results. Finally, only patients from European countries and Australia were included in the current study. The relative efficacy and safety of dPDT and cPDT in patients

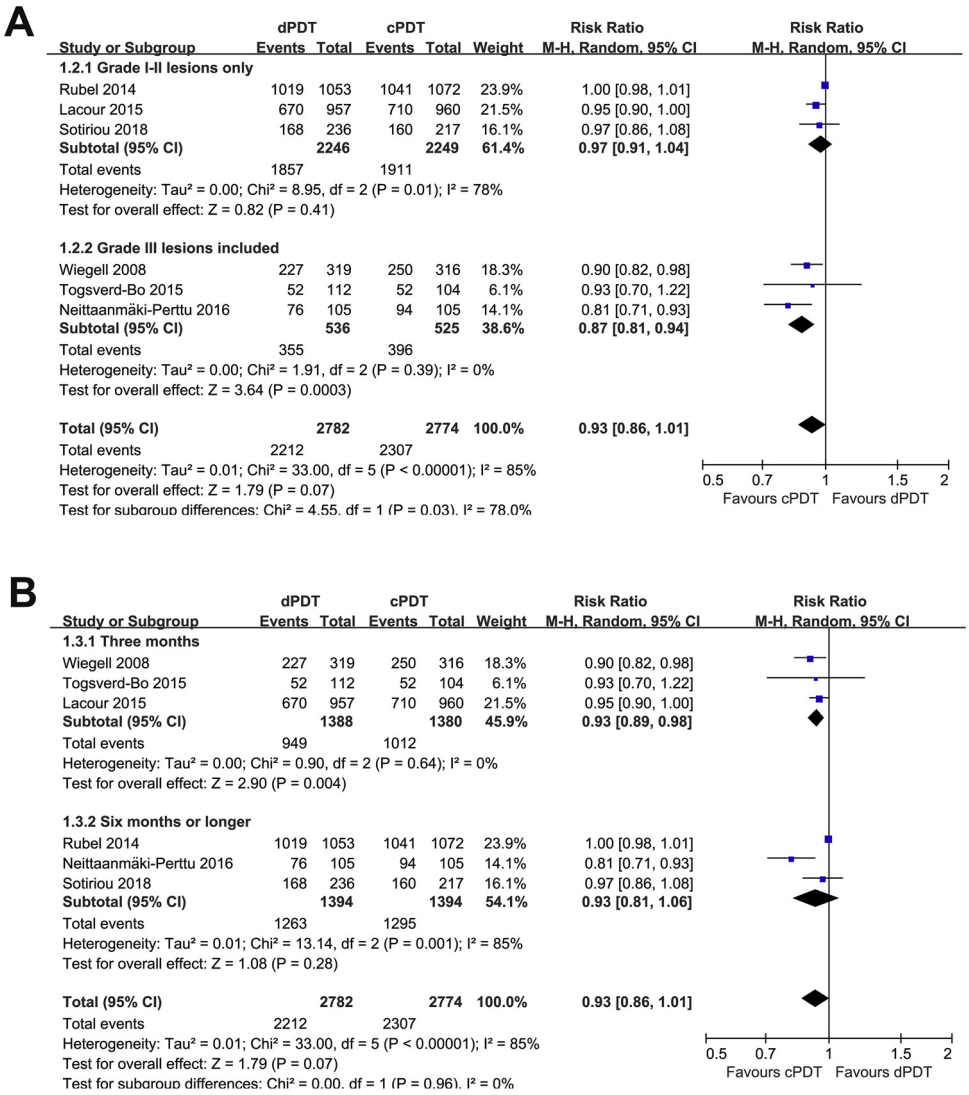

Fig. 3. Subgroup analyses for the meta-analysis comparing the efficacy of daylight photodynamic therapy (dPDT) and conventional photodynamic therapy (cPDT) on the complete response (CR) of the actinic keratosis (AK) lesions. A, subgroup analysis according to the grade of AK lesions; B, subgroup analysis according to the follow-up durations.

with AK from different countries, such as China [30], should also be evaluated.

In conclusion, the results of our meta-analysis indicated that, although dPDT is better tolerated, the treatment efficacy of dPDT is non-inferior to cPDT with red light and MAL in grade I-II AK lesions. The relative therapeutic efficacy of dPDT and cPDT in patients with AK

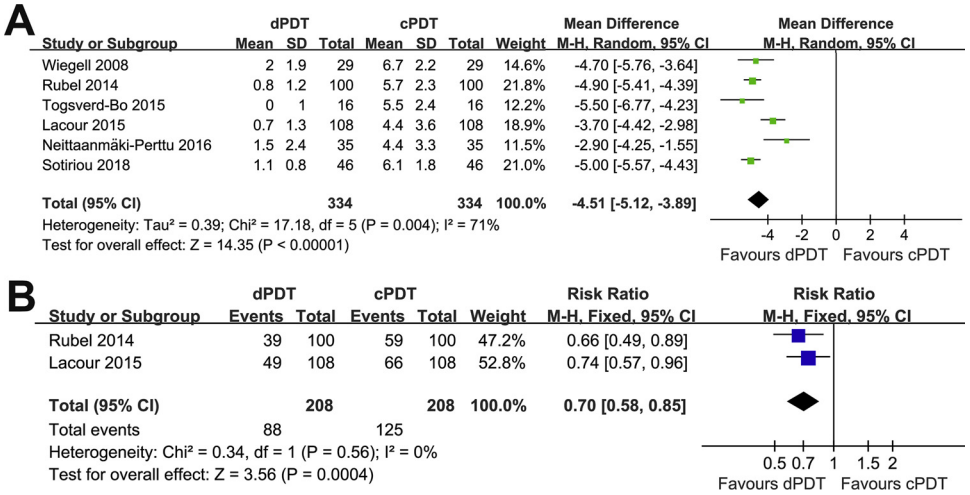

Fig. 4. Forest plots comparing the safety outcomes of daylight photodynamic therapy (dPDT) and daylight photodynamic therapy (cPDT) in patients with actinic keratosis (AK). A, forest plots comparing the influences of dPDT and cPDT on the maximal pain scores; B, forest plots comparing the influences of dPDT and cPDT on the incidences of adverse side effects (AEs).

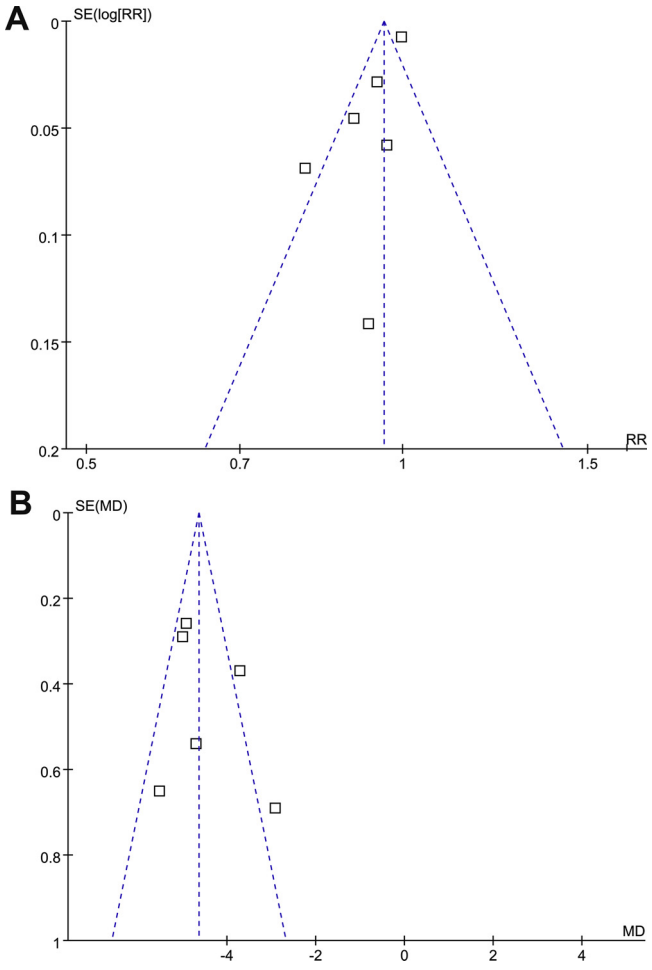

Fig. 5. Funnel plots for the meta-analyses. A, funnel plots for the meta-analysis comparing the efficacy of daylight photodynamic therapy (dPDT) and conventional photodynamic therapy (cPDT) on complete response (CR) of the actinic keratosis (AK) lesions; B, funnel plots for the meta-analysis comparing the influences of dPDT and cPDT on the maximal pain scores; For outcome of categorized variable as in Fig. 5A, risk ratios (RRs) and the standard errors of log-transformed RRs from each included study were plotted to form the funnel plots; while for outcome of continuous variable as in Fig. 5B, mean differences (MDs) and the standard errors of MDs from each included study were plotted to form the funnel plots. Each transparent square indicates an included study.

with grade III lesions should be further evaluated.

Conflict of interest

The authors have no conflicts of interest to report.

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