Laser-assisted photodynamic therapy for actinic keratosis: A systematic review and meta-analysis

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Background: Photodynamic therapy (PDT) is an effective intervention for actinic keratosis and field cancerization. Ablative fractional lasers may facilitate the delivery of photosensitizers and thereby improve the effects of PDT.

Objective: To summarize the current evidence on the efficacy and safety of laser-assisted PDT.

Methods: We performed a systematic literature research in Medline, Embase, and the Cochrane Central Register of Controlled Trials and hand-searched pertinent trial registers for eligible randomized controlled trials. Results from individual studies were pooled by using a random-effects model. The risk of bias was estimated with the Cochrane Risk of Bias Tool, and the quality of evidence of the outcomes was assessed with the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: Of 817 records initially identified, 7 randomized controlled trials were included in the qualitative analysis and 4 were included in the meta-analysis. Laser-assisted PDT showed significantly higher clearance rates than did PDT monotherapy (risk ratio, 1.33; 95% confidence interval, 1.24-1.42; I^2 = 25%; $P < .01$). There was no difference in pain intensity between laser-assisted PDT and other interventions (mean difference, 0.31; 95% confidence interval, −0.12 to 0.74; I^2 = 0%; $P = .16$). The included studies showed a high risk of bias.

Limitations: The clinical heterogeneity of included studies.

Conclusion: Laser-assisted PDT is more efficient but not more painful than PDT or laser treatment only. (J Am Acad Dermatol 2019;80:947-56.)

Key words: actinic keratosis; carbon dioxide laser; erbium:yttrium-argon-garnet laser; general oncology; meta-analysis; photodynamic therapy; senile keratosis; solar keratosis; systematic review.

Actinic keratoses (AKs) are precancerous lesions of the skin as a consequence of long-term sun exposure.[1,2] They can progress into cutaneous squamous cell carcinoma (cSCC), although the risk is presumably low.[3] International guidelines recommend the treatment of AKs because predicting whether a lesion will become invasive cSCC is not possible.[4]

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) or its ester methyl-aminolevulinate (MAL) is a highly effective treatment for multiple AKs or field cancerization with an excellent cosmetic outcome.[5,6]

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However, 1 of the main side effects is local pain during illumination, which can limit treatment adherence and patient satisfaction.[7] Other limiting factors include the thickness of the individual lesions, as hyperkeratotic lesions are poorly penetrated by the photosensitizing agent, requiring pretreatment with curettage before PDT.

PDT as a field-directed approach may be combined with lesion-targeted pretreatment by ablative and nonablative laser devices (laser-assisted PDT). An ablative fractional laser (AFXL) creates microscopic vertical channels that may facilitate the penetration and enrichment of ALA or MAL in dysplastic cells, a concept that has been termed *laser-assisted drug delivery*. However, whether laser-assisted PDT is really more effective than PDT alone has been a subject of debate, and clear-cut evidence from randomized controlled trials (RCTs) is lacking. Here, we have performed a systematic review to summarize the current evidence for laser-assisted PDT for AK.

CAPSULE SUMMARY

- This meta-analysis suggests that photodynamic therapy combined with ablative laser treatment for actinic keratosis is more efficient but not more painful than either therapy alone.
- Laser-assisted photodynamic therapy is an attractive option for patients with multiple actinic keratoses or field cancerization.

MATERIALS AND METHODS

Protocol and registration

The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=87854). The register identifier is PROSPERO 2018 CRD42018087854. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[8] and the Cochrane Handbook For Systematic Reviews.[9]

Eligibility criteria

Patients with the clinical and/or histopathologic diagnosis of AK were included. They were to be treated with a combination of PDT and laser therapy. Both MAL and ALA were allowed as photosensitizers. Ablative and nonablative laser devices were eligible. We included only RCTs in which study participants (interindividual trials) or entire body parts (intraindividual trials) were investigated. Pseudorandomized trials, observational studies, retrospective studies, crossover studies, and case series were excluded.

Search strategy and data sources

We searched the electronic databases Medline and Embase (both via Ovid) as well as the Cochrane Central Register of Controlled Trials to identify all relevant records until January 24, 2018. Additionally, we searched the following trial registers for the keywords *actinic keratosis* or *actinic keratoses*: the metaRegister of Controlled Trials (ISRCTN registry [www.controlled-trials.com]), US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch/), and European Union Clinical Trials Register (www.clinicaltrialsregister.eu/); the last search was conducted on February 20, 2018. For ongoing trials and completed trials without data publication, principal investigators or trial sponsors were contacted to obtain preliminary or unpublished data. Reference lists of the included records were screened.

Study selection

Two authors (J.G.S. and T.S.) independently screened the titles and abstracts identified in the electronic database searches to determine their eligibility. Trial registers were hand-searched and assessed for eligibility by 1 author (T.S.). For records that were considered relevant according to the title and abstract screening, full-text articles were obtained and the inclusion and exclusion criteria were applied. Whenever discrepancies arose, resolution was achieved by discussion with a third independent author (M.V.H.).

Outcomes

The primary outcomes were the lesion-specific complete clearance rate and local adverse events), as determined by the number of patients or treated areas with skin irritation. Secondary outcomes were cosmetic outcome, which was quantified as the number of patients or treatment areas with skin dyspigmentation; patient satisfaction, which was rated globally as "satisfied" or "very satisfied"; and pain as a result of treatment, which was reported on a visual analogue scale from 0 (none) to 10 (extreme pain). All outcomes had to have been reported at

Abbreviations used:

AFXL:	ablative fractional laser
AK:	actinic keratosis
ALA:	5-aminolevulinic acid
CI:	confidence interval
cSCC:	cutaneous squamous cell carcinoma
dPDT:	photodynamic therapy with daylight
MAL:	methyl-aminolevulinate
OTR:	organ transplant recipient
PDT:	photodynamic therapy
RCT:	randomized controlled trial
RR:	risk ratio

least 2 months but no more than 6 months after the end of treatment.

Data collection, synthesis, and management

Information regarding each of the included study's design, baseline characteristics, intervention, risk of bias, and primary and secondary outcomes was collected and summarized by 2 authors independently (T.S. and J.G.S.) with the use of RevMan 5.3 software.[10]

Wherever possible and suitable, we performed a meta-analysis of quantitative data by using RevMan 5.3.[10] We used the random-effects model, as clinical and methodologic heterogeneity between the studies was likely. We expressed dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous outcomes as mean differences with 95% CIs. To analyze the lesion-specific clearance rate in intraindividual trials, we considered the lesions of a given treatment randomized as a cluster. To address the influence on the effect estimate, we performed sensitivity analysis by repeating meta-analysis with only interindividual trials. Where possible, we calculated the data following the intention-to-treat principle. If meta-analysis for an outcome was impossible, we described the results qualitatively (Table I[11-17]).

Risk of bias assessment and quality of evidence assessment

Two authors (J.G.S. and T.S.) independently assessed the risk of bias of the included studies with the Cochrane Risk of Bias Tool.[9] Discrepancies were thoroughly discussed and resolved with the full texts and supplementary material. The quality of evidence for each outcome was rated by the same authors by using GRADEpro Guideline Development Tool software (www.gradepro.org).[18] If at least 10 RCTs reported a specific comparison, we intended to assess publication bias by creating a funnel plot.

RESULTS

Study identification

Our literature search identified 817 references; 14 records underwent full-text review after title and abstract screening and removal of duplicates. Seven records were excluded because they had an uncontrolled design,[19] did not meet the inclusion criteria,[20-22] or did not present any relevant data.[23,24] One more duplicate was identified[25] (Fig 1). Finally, 7 RCTs with a total sample size of 240 met the eligibility criteria. Of the 7 studies, 6 assessed MAL[12-17] and 1 assessed ALA[11] as a photosensitizer. Regarding the type of laser, 3 studies investigated an erbium:yttrium-argon-garnet laser[12,14,17] and the remaining 4 investigated a carbon dioxide (CO_2) laser.[11,13,15,16]

Clearance rates

Six studies comparing the reported clearance rates achieved by use of laser-assisted PDT with those achieved by use of PDT monotherapy.[11,12,14-17] Of the 6 studies, 4 provided sufficient data to perform meta-analysis (Fig 2).[11,12,14,16] Laser-assisted PDT showed significantly higher clearance rates than did PDT monotherapy (RR, 1.33; 95% CI, 1.24−1.42; I^2 = 25%; $P < .01$). A sensitivity analysis with interindividual trials only revealed a similar effect (RR, 1.41; 95% CI, 1.27-1.56; I^2 = 0%).

Song et al reported data from an interindividual study with 46 participants.[15] Conventional PDT plus AFXL was more efficient than PDT monotherapy (clearance rate, 71.4% vs 64.7% [the difference was not statistically significant]). In an intraindividual trial with 16 organ transplant recipients (OTRs), Togsverd-Bo et al compared the combination of daylight PDT (dPDT) and AFXL with dPDT or conventional PDT as monotherapy.[17] The areas treated with AFXL and dPDT, dPDT alone, and conventional PDT alone showed median complete response rates of 74% (range, 37%−100%), 46% (range, 0%−75%), and 50% (range, 25%−83%), respectively (a statistically significant difference). We rated the quality of evidence as low (Table II).

Local skin irritation

None of the studies reported severe adverse events or cases in which patients had to discontinue treatment.

Dyspigmentation

Dyspigmentation was inconsistently reported. Because of substantial heterogeneity among the trials, we did not perform meta-analysis. The data provided by Choi et al could not be analyzed on

Table I. Overview of the reported outcomes of the included studies

Reference	Laser and/or PDT interventions	Primary outcomes		Secondary outcomes		
		Efficacy lesion clearance, % (n/N)	Local adverse events	Skin dyspigmentation, % (n/N)	Patient satisfaction	Pain, VAS score
Alexiades[11] (2017)	ALA PDT+ CO_2 laser	87.81% (54/443)	Unclear	0% (0/10)	NR	mean, 4
	ALA PDT	70.09% (131/438)	Unclear	0% (0/10)	NR	mean, 3
Choi et al[12] (2015)	Er:YAG laser + 2 h of MAL PDT	76.8%; 95% CI 70.1-83.6% (116/151)	Unclear	Unclear	NR	mean ± SD, 5.91 ± 1.27
	Er:YAG laser + 3 h of PDT	91.7%, 95% CI 87.2-96.2%, (133/145)	Unclear	Unclear	NR	mean ± SD, 6.06 ± 0.71
	3 h of MAL PDT	65.6%, 95% CI 57.5-73.8% (86/131)	Unclear	Unclear	NR	mean ± SD, 5.77 ± 1.13
Helsing et al[13] (2013)*	CO_2 laser + MAL PDT	73% (range, 8%-57%)	Unclear	30% (3/10)	NR	NR
	CO_2 laser	31% (range, 8%-57%)	Unclear	10% (1/10)	NR	NR
Ko et al[14] (2014)	Er:YAG laser + MAL PDT	86.9% (93/107)	Unclear	100% (20/20)	NR	mean ± SD, 4.765 ± 2.283
	MAL PDT	61.2% (79/129)	Unclear	100% (20/20)	NR	mean ± SD, 4.304 ± 1.714
Song et al[15] (2015)	CO_2 laser + MAL PDT	71.4%	NR	NR	NR	NR
	MAL PDT	64.7%	NR	NR	NR	NR
Togsverd-Bo et al[16] (2012)	CO_2 laser + MAL PDT	90% (93/103)	Unclear	40% (6/15)	NR	median, 6.5 (range, 2-10)
	MAL PDT	67% (71/109)	Unclear	13.3% (2/15)	NR	median, 5.5 (range, 3-8)
Togsverd-Bo et al[17] (2015)	Er:YAG laser + dPDT	74% (range, 37%-100%)	NR	0% (0/16)	NR	median, 0 (range, 0-3)
	dPDT	46% (range, 0%-75%)	NR	0% (0/16)	NR	median, 0 (range, 0-1)
	MAL PDT	50% (range, 25%-83%)	NR	0% (0/16)	NR	median, 5.5 (range, 3-9)
	Er:YAG laser	5% (range, 0%-40%)	NR	0% (0/16)	NR	median, 0

ALA PDT, Photodynamic therapy with 5-aminolevulinic acid, *CI*, confidence interval, *CO_2*, carbon dioxide, *dPDT*, daylight photodynamic therapy; *Er:YAG*, erbium:yttrium-argon-garnet; *MAL PDT*, photodynamic therapy with methyl aminolevulinate; *NR*, not reported; *OTR*, organ transplant recipient; *SD*, standard deviation; *VAS*, visual analogue scale.
*This study was identified according to the review protocol but is not reported because it compared laser-assisted PDT with laser monotherapy.

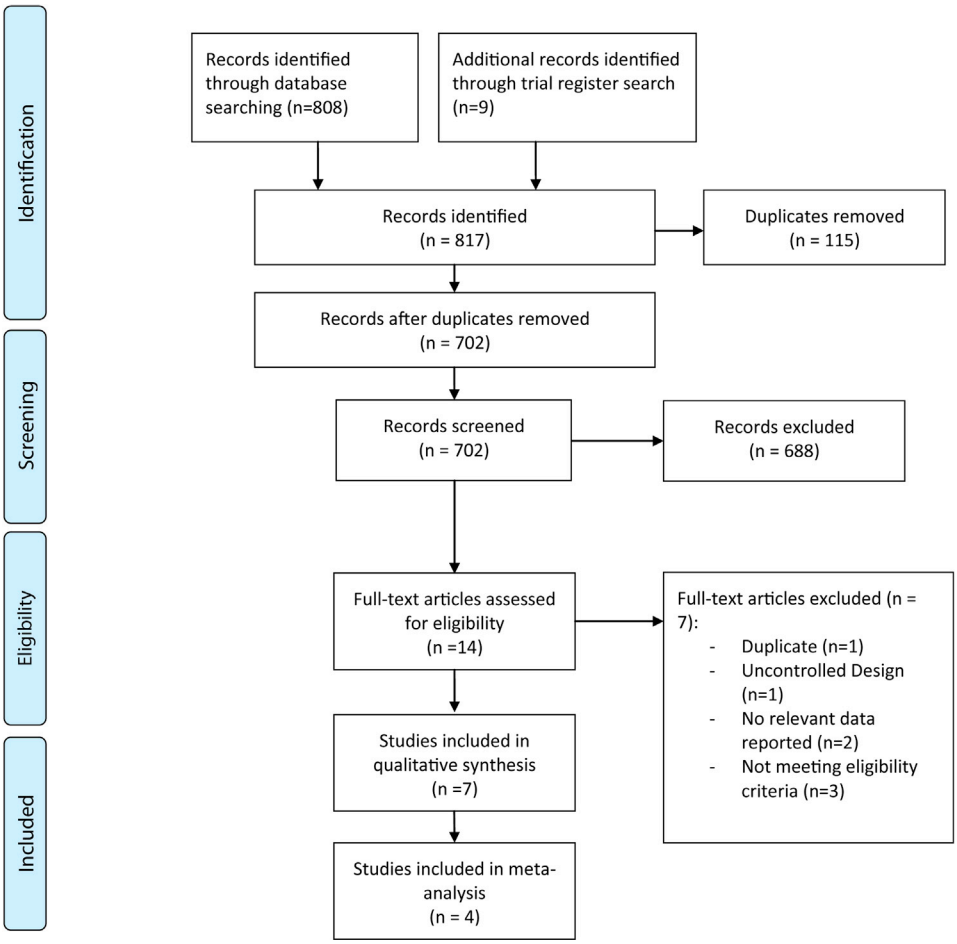

Fig 1. Selection process for study inclusion in the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

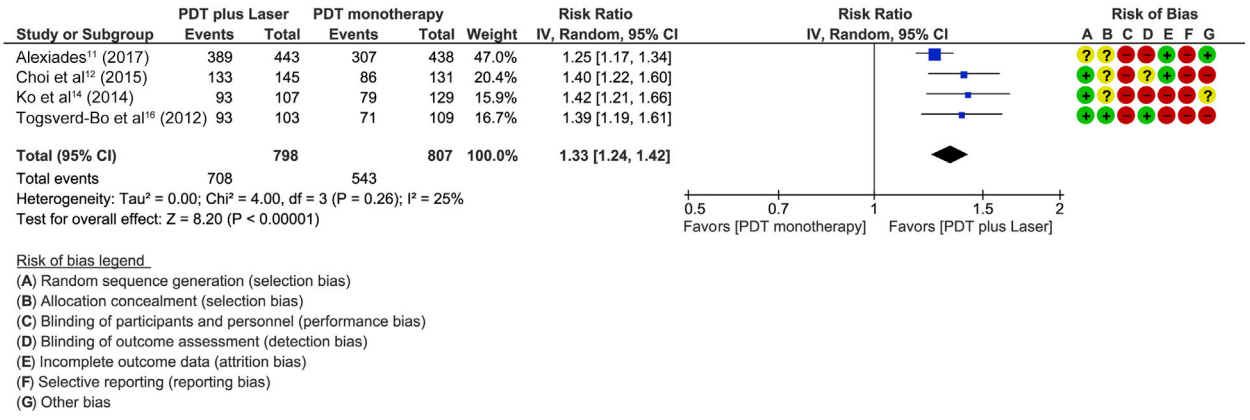

Fig 2. Risk ratio to have actinic keratoses cleared for the intervention laser-assisted photodynamic therapy (PDT) compared with that for PDT monotherapy. This is a forest plot examining randomized controlled trials. Random-effects analysis was used. The diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). *df*, Degrees of freedom; *IV*, instrumental variable.

account of incoherent reporting.[12] In 2 intraindividual studies with 10 and 16 patients, respectively, no dyspigmentation occurred.[11,17] An interindividual trial (N = 40) reported that all participants experienced dyspigmentation, irrespective of the intervention.[14]

Table II. Summary of evidence table for the outcomes of the comparison laser-assisted PDT versus PDT monotherapy for patients with AK

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence, on a scale of 1 to 4 (GRADE approach)	Comments
	Risk with PDT monotherapy	Risk with laser-assisted PDT				
Clearance rate	673 per 1000	895 per 1000 (834-955)	RR 1.33 (1.24-1.42)	1605 (4 RCTs)	2 (low)†	Laser-assisted PDT appears to reduce clearance rate. Of note: 1605 treatment areas were randomized, not participants. The 4 RCTs included a total of 129 patients; 25 patients were included in 2 studies with an intraindividual design (ie, the participants served as their own control). The remaining 2 studies had an interindividual design with 52 participants in the intervention group and 53 in the control group.
Skin irritation—not reported	None of the included RCTs specifically reported this outcome			-	-	-
Dyspigmentation	In 2 studies, with 10 and 16 patients, respectively, no dyspigmentation occurred. Another trial (N = 40) reported that all participants experienced dyspigmentation, irrespective of treatment. Another trial reported that dyspigmentation was observed in 6 laser-assisted PDT and in 2 PDT only areas. One study did not provide sufficient data regarding dyspigmentation			(5 RCTs)	1 (very low)‡§	We are uncertain about the effect of laser-assisted PDT on dyspigmentation.

Patient satisfaction—not reported	None of the included RCTs specifically reported this outcome.		-	-	-	
Pain assessed with VAS scale (0-10)	The mean pain score was 0	The mean pain score in the intervention group was 0.31 higher (0.12 lower to 0.74 higher)	-	104 (2 RCTs)	2 (low)[‖]	Laser-assisted PDT may result in a small effect that may not be an important (or unimportant) reduction in pain.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group grades of evidence are as follows: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low certainty, our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect); and very low certainty, we have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of the effect).

AK, Actinic keratosis; *CI*, confidence interval; *RCT*, randomized controlled trial; *PDT*, photodynamic therapy; *RR*, risk ratio; *VAS*, visual analogue scale.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[†]For the study by Alexiades et al,[11] whether the outcome assessment was done in blinded fashion remains unclear. In addition, the study by Ko et al[14] had an open-label design; therefore, detection bias is likely. Dropouts in the laser-assisted PDT group imbalanced the baseline disease severity of the intervention groups. The study of Togsverd-Bo et al[16] was at risk of attrition bias because the results are probably reported for only 12 of 15 patients. Besides, 14 of 15 patients received prior treatment of their AKs, but the authors did not specify the nature and duration of the previous therapy (which may have had an impact on the study results even though the AK treatment had to have ended 4 weeks before the study according to their eligibility criteria). Overall, the studies showed a high risk of bias (−2).

[‡]All studies showed a high risk of performance bias. The studies by Alexiades et al[11] and Ko et al[14] also had a high risk of detection bias, whereas the risk of detection bias for the study by Choi et al[12] remains unclear (−2).

[§]The results were highly inconsistent. In the studies of Alexiades et al[11] and Togsverd-Bo et al[17] no dyspigmentation was reported among the participants (N = 26 [intraindividual design]), whereas Ko et al[14] reported all patients as showing dyspigmentation (N = 40 [interindividual design]).

[‖]Both studies show a high risk of performance bias. Additionally, the study of Ko et al[14] also has a risk of detection bias because of its open-label design (−2).

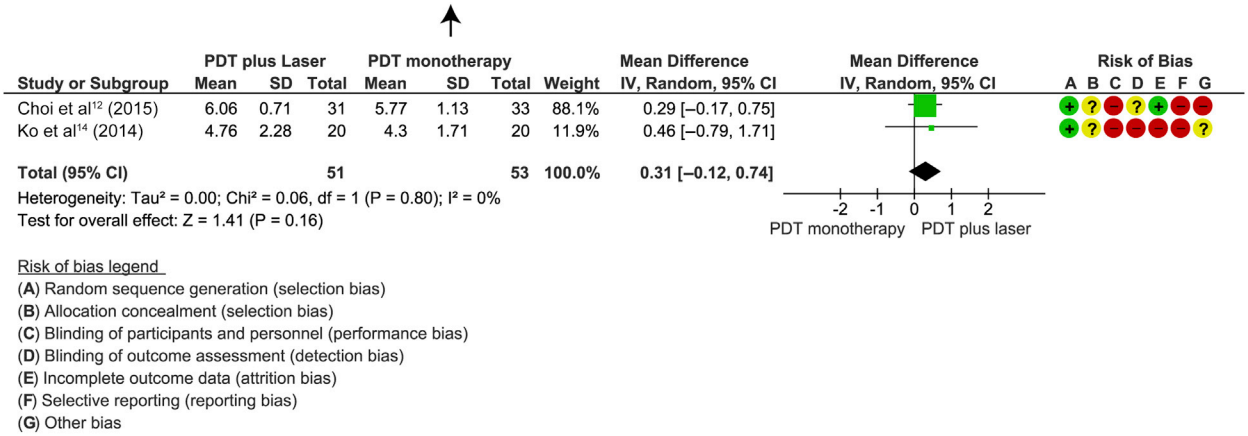

Fig 3. Mean differences in pain intensity for the intervention laser-assisted photodynamic therapy (PDT) versus for PDT monotherapy, as assessed on a visual analogue scale. This is a forest plot examining randomized controlled trials with an interindividual design. Random-effects analysis was used. The diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). *df*, Degrees of freedom; *IV*, instrumental variable; *SD*, standard deviation.

Togsverd-Bo et al reported in an intraindividual trial with 15 patients that dyspigmentation was observed in 6 and 2 areas treated with AFXL-PDT and PDT, respectively.[16] The quality of evidence was rated as very low (Table II[11,12,14,16,17]).

Patient satisfaction

None of the included studies reported this outcome.

Pain

Five studies measured the severity of pain during or immediately after treatment. Two studies with an interindividual design and 104 participants provided sufficient data for meta-analysis, showing no difference in pain intensity between the 2 interventions (mean difference, 0.31; 95% CI, −0.12 to 0.74; I^2 = 0%; P = .16) (Fig 3).[12,14] One intraindividual trial with 10 participants reported an average pain intensity score of 4 on the visual analogue scale for the combination therapy and an average score of 3 for PDT monotherapy.[11] However, the authors did not report either CI or whether the effect was significant. In an intraindividual study with 15 patients, Togsverd-Bo et al reported a median pain intensity score of 6.5 (range, 2-10) on the side treated with combination therapy and a median score of 5.4 (range, 3-8) on the area treated with PDT (P = .023).[16]

Another intraindividual study showed that there was no difference in pain intensity between the combination of laser and dPDT (median, 0; range, 0-3) compared with dPDT alone (median, 0; range, 0-1) among 16 OTRs.[17] The quality of evidence was rated as low (Table II).

Bias assessment

As we included fewer than 10 studies, we did not create a funnel plot and cannot exclude the presence of publication bias. None of the studies provided any cause for serious suspicion of selection bias. Blinding of participants was not performed, which may have resulted in performance bias for subjective outcomes such as pain. Blinding of the outcome assessor was clearly stated in 3 trials. Most studies were free of attrition bias. However, 2 studies had a dropout rate of more than 10% without performance of intention-to-treat analysis. These studies were at high risk of attrition bias. We identified a high risk of selective reporting bias, mostly because trials either reported only P values without providing further statistical data or did not adequately report results for predefined outcomes.

DISCUSSION

Our results suggest an increased effectiveness of laser-assisted PDT regarding lesion clearance; however, the certainty of the evidence was considered low according to evaluation based on the Grading of Recommendations, Assessment, Development, and Evaluation approach. The increased efficacy of AFXL used as an adjunct to PDT may be explained by 2 different mechanisms. First, laser ablation creates vertical microchannels within the stratum corneum

that facilitate penetration of the photosensitizer and accumulation of protoporphyrin IX.[26,27] Second, AFXL treatment has direct cytotoxic effects on target cells. Despite growing evidence that nonablative devices can also be used with high clearance rates for AK, no trial met the inclusion criteria applied here. Meta-analysis was possible for lesion clearance for the comparison of laser-assisted PDT versus PDT monotherapy, revealing an RR of 1.33 in favor of the combination therapy. A 33% higher chance of lesion clearance is remarkable, as PDT alone is considered a highly effective treatment for AKs and has shown clearance rates of 70% to 90% in several phase III trials. This risk estimate, however, needs to be interpreted with caution owing to high clinical heterogeneity regarding differences in the treatment protocols, variability of the settings of the lasers used, and the fact that some studies were designed as interindividual trials while others were designed as intraindividual trials.

From a methodologic perspective, it is not single AK lesions but treatment areas that are subject to randomization in intraindividual trials. Although individual lesions were not randomized to the specific treatments, we considered them randomized as a cluster for the analysis. Intercluster correlation coefficients were not reported in any trial. Thus, cluster effects of the included studies remain unclear and represent a possible source of bias for the results regarding the lesion-specific response. When only trials with an interindividual design were analyzed, similar results were obtained, underlining the fact that the observed effect is consistent. Furthermore, the results regarding the lesion-specific response may be underpowered. Assessment at the level of individual lesions can falsely inflate the power because it is usually calculated on the basis of the study participants and not on basis of the total number of AK lesions. However, this is a statistical pitfall that arises at the individual trial level, where reporting lesion-specific response rates without further statistical adjustments seems to be common practice.

Regarding tolerability, in most trials, reporting of patient satisfaction, local skin reactions, and dyspigmentation was poor. Thus, we are uncertain of and cannot draw clear conclusions regarding these outcomes. In contrast, pain was well documented. Laser-assisted PDT was not perceived as more painful than PDT only, regardless of whether it was conducted after illumination from light-emitting diodes or in natural daylight (which is a nearly painless alternative to conventional PDT).[28,29]

Two studies investigated OTRs as their population. Because of long-term immunosuppression with reduced immune surveillance, AKs are more likely to progress to cSCC and show lower response to therapy.[30] Although a subgroup analysis was not performed here, the studies performed by Helsing et al and Togsverd-Bo et al showed significantly higher rates of lesion clearance for the combination.[13,17] The low clearance rates observed with PDT only in this study imply that monotherapy may not be sufficient for AK clearance and suggest that laser-assisted PDT should be preferred in OTRs or for difficult-to-treat lesions.

All together, our study showed that ablative laser-assisted PDT provided a higher likelihood of lesion clearance than PDT alone without a significant difference regarding pain. Thus, it may be offered upfront for difficult-to-treat AKs such as hyperkeratotic, acral lesions, or AKs in OTRs.

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