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Efficacy and safety of photodynamic therapy with amino-5-laevulinate nanoemulsion versus methyl-5-aminolaevulinate for actinic keratosis: A meta-analysis

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ABSTRACT

Background: Photodynamic therapy is an effective treatment for actinic keratosis. 5-aminolevulinic acid nanoemulsion (BF-200 ALA) and methyl-5-aminolevulinate (MAL) are both prodrugs for the treatment of actinic keratosis with photodynamic therapy. A comparison of the efficacy and safety between the drugs is critical for clinical practice.

Objectives: To investigate if photodynamic therapy in combination with BF-200 ALA is superior to photodynamic therapy with MAL for actinic keratosis.

Methods: We performed a meta-analysis to investigate the combination of photodynamic therapy with BF-200 ALA and with MAL. The PubMed, Cochrane Library, Web of Science and EMBASE databases were searched to select eligible randomized controlled trials. Our search was conducted on April 1, 2019, and included the search terms "5-aminolevulinic acid nanoemulsion or BF-200 ALA", "methyl-5-aminolevulinate or methyl aminolaevulinate" and "actnic keratosis". Cochrane Risk of Bias Tool was used to estimate the risk of bias.

Results: The meta-analysis consisted of 5988 actinic keratosis lesions in five eligible randomized controlled trials, with a total of 2953 actinic keratosis lesions treated with BF-200 ALA and 3035 actinic keratosis lesions treated with MAL. BF-200 ALA in combination with photodynamic therapy showed significantly higher overall complete clearance rates (RR: 1.07, 95% CI 1.02–1.12, $p = 0.01$) and 3 month complete clearance rates (RR: 1.09, 95% CI 1.06–1.12, $p < 0.00001$) compared to MAL. A subgroup analysis was performed for photodynamic therapy combined with BF-200 ALA, revealing increased complete clearance rates of grade II-III lesions in comparison with MAL (RR: 1.24, 95% CI 1.05–1.46, $p = 0.01$). Compared with MAL, the pooled relative risk for the meta-analysis for recurrence was 0.67 (95% CI 0.48-0.92, $p = 0.01$) at 12 month after BF-200 ALA treatment.

Conclusion: Photodynamic therapy with BF-200 ALA has a 9% better chance of complete clearance at 3 months and a 24% better chance of grade II-III lesions after treatment than with MAL for patients with actinic keratosis.

1. Introduction

Actinic keratosis is the premalignant stage of cutaneous squamous cell cancer and occur mainly on face, bald scalp, neck and arms. [1] Approximately 65% of all primary squamous cell cancers developed from previously diagnosed actinic keratosis [2]. In clinical, the presence of multiple actinic keratosis in one region may reflect neoplastic changes [3]. Consequently, different stages of actinic keratosis could exist in the cancerous field, including visible and non-visible subclinical lesions, early-clinical and late-clinical lesions, and invasive squamous cell carcinoma [4].

Photodynamic therapy (PDT) was recommended as first-line therapeutic modality for actinic keratosis [5] owing to its high rates of efficacy and improved cosmetic outcomes [6]. 5-aminolevulinic acid (ALA), a topical porphyrin precursor, leaded to the local accumulation of endogenous photosensitizer protoporphyrin IX (PpIX) [7]. PDT combined with ALA had been shown to achieve excellent results compared with PDT plus placebo [8,9].

However, the complete clearance rates of PDT with ALA for actinic keratosis remained to be elevated. Several ALA-based topical

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medications had been used, differing in regard to additional chemical modifications and other vehicle compositions. Two photosensitizers had been studied for use in PDT: Methy-5-laminolevulinate (MAL) and ALA-nanoemulsion (BF-200 ALA). MAL, a lipophilic derivative of ALA that showed no significant difference between MAL and ALA. [10] On the contrary, BF-200 ALA, a new nanoemulsion-based gel formulation containing 7.8% ALA, enhanced the penetration into the stratum corneum [11] and was found to be a very effective new formulation for the treatment of actinic keratosis with PDT [12].

In previous studies comparing BF-200 ALA and MAL when used in PDT for actinic keratosis, BF-200 ALA was prone to show better efficacy. [13–19] The aim of the present meta-analysis was to verify the results of current knowledge by comparing the efficacy and safety of BF-200 ALA and MAL in PDT for actinic keratosis.

2. Methods

2.1. Protocol and registration

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. [20]

2.2. Eligibility criteria

Eligibility was restricted to trials with human participants only and a randomized controlled study design. Patients were clinical and/or histologic diagnosed as actinic keratosis. They were to be treated with photosensitizers (BF-200 ALA or MAL) followed a combination of PDT. Both inter-individual trials and intra-individual trials were investigated. Single arm and placebo-controlled trials were excluded.

2.3. Search strategy and databases

We systematically searched the electronic databases PubMed, Cochrane Library, Web of Science and EMBASE to identify all relevant records until April 1, 2019. Additionally, search terms included “actinic keratosis”, “5-aminolevulinic acid nanoemulsion or BF-200 ALA” and “methyl-5-aminolevulinate or methyl aminolaevulinate”. No restrictions were used for the search string. The results were uploaded into a citation database program for review (EndNote: http://endnote.com/).

2.4. Selection process

Two authors (CF and BW) independently screened titles and abstracts for eligible studies that identified in the electronic database searched. Trial registers were hand-searched and assessed for eligibility by one author (BW). For records that were considered relevant according to title and abstract screening, full-text articles were obtained and checked by two review authors independently (CF and LQ) for inclusion and exclusion criteria. Whenever discrepancies arose, resolution was achieved by discussion.

2.5. Outcomes

The primary outcomes were: 1. the participant complete clearance rate, defined as the rate of participants who had completely reduction of lesion counts from baseline to assessment (absolute values); 2. the participant recurrence rate. The secondary outcomes were pain due to treatment, reported on a visual analogue scale (VAS) from 0 to 10.

2.6. Data collection, synthesis and management

Information on each included randomized controlled trial regarding study design, baseline characteristics, outcomes, types of intervention and risk of bias were collected and summarized by two authors independently (CF and BW) using Review Manager Version (RevMan 5.3). Wherever possible and suitable, we performed a meta-analysis of quantitative data using RevMan 5.3. Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI), and continuous outcomes as mean or median differences (MD) with 95% CI. Random-effects model was applied if the heterogeneity test showed statistical significance ($p < 0.10$, $I^2 > 50\%$).

2.7. Risk of bias assessment

Two authors (BK and XZ) independently assessed the risk of bias of the included trials with the Cochrane Risk of Bias Tool. Discrepancies were thoroughly discussed and resolved through using the details providing by the full texts and supplementary material.

3. Results

3.1. Study screening

Our search of the PubMed, Cochrane Library, Web of Science and EMBASE databases identified 52 publications and meeting abstracts. We then excluded 24 duplicates. We excluded 13 after review of titles and abstracts demonstrated irrelevant topics, non-comparative studies and case reports. 15 records underwent full-text review. Eight records were excluded because they were reviews or comments (n = 4) or because they were unpublished trials (n = 4). Finally, a total of 7 studies [13–19] met the eligibility criteria, including 5 randomized controlled trials and two long-term follow-up studies (Fig. 1).

3.2. Study and participant characteristics

Overall, 5 randomized controlled trials in 7 records with a total sample size of 678 patients with 5988 actinic keratosis lesions. The characteristics of the eligible trials were summarized in Table 1. Three of the five trials were conducted at multicenter sites. Follow-up duration ranged from 1 month to 12 months. Most participants in these comparative trials were older and tended to favor male enrollment. Mean age of study participants ranged from 70.7 to 79.8 years with the fraction of male participants ranging from 54% to 96%. Locations

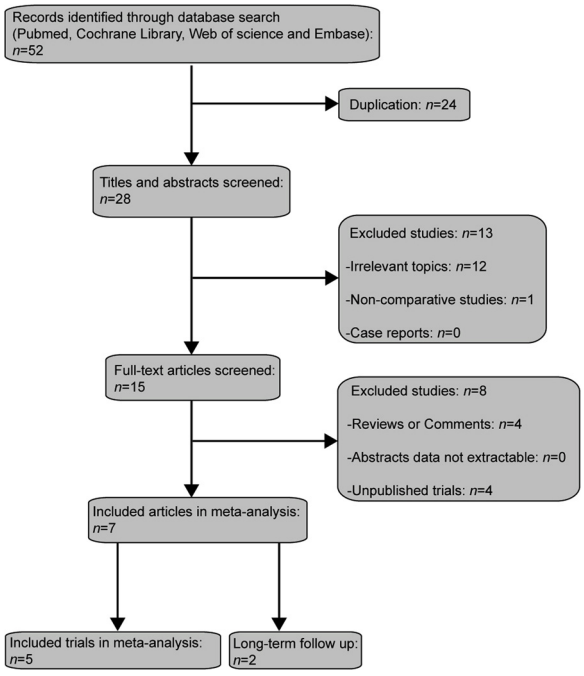

Fig. 1. Flow diagram of the literature search.

Table 1
Characteristics of randomized clinical trials in the meta-analysis.

Source	Year	Center	No. of Patients	No. of Lesions	Grade (No. B + M)	Age (mean, y)	No. of Male	Location	Incubation time (h)	Light Source	Exposure time (h)	Length of Follow-up
C. Serra-Guillén	2018	Single-	50	BF-200 ALA: 674 MAL: 681	NR	72.2	48	Face/scalp	3	Aktilite CL 128	NR	1 month
J. E. Räsänen	2018	Multi-	69	BF-200 ALA: 375 MAL: 392	I: 278 + 299 II-III: 97 + 93	74.8	43	Face/scalp	0.5	daylight	2	12 month
N.Neittaanmäki-Perttu	2014/2016	Single-	13	BF-200 ALA: 84 MAL: 93	I: 61 + 73 II-III: 23 + 20	79.8	7	Face/scalp	0.5	daylight	2	12 month
T. Dirschka	2012/2013	Multi-	494	BF-200 ALA: 1504 MAL: 1557	I: 624 + 564 II-III: 880 + 993	70.7	419	Face/scalp	3	Aktilite CL 128 Omnilux PDT PhotoDyn 750 /505	NR	12 month
T. Dirschka	2019	Multi-	52	BF-200 ALA: 316 MAL: 312	I: 154 + 154 II-III: 162 + 158	72.2	50	Face/scalp	0.5	daylight	2	12 month

Abbreviations: BF-200 ALA5-aminolevulinic acid nanoemulsion; MALmethyl-5-aminolevulinate; B + M5-aminolevulinic acid nanoemulsion + methyl-5-aminolevulinate; No.number of patients; NRnot reported.

included the face and scalp in the selected trials. Daylight illumination was applied in three trials. One trial used only Aktilite CL 128 as light source, and one multicenter trial used Aktilite CL 128, Omnilux PDT or PhotoDyn 750/705 as the light source.

3.3. Complete lesion response

All of the selected trials reported the complete clearance of actinic keratosis lesions. Compared with MAL photodynamic therapy, the pooled relative risk for the complete lesion response was significantly higher after BF-200 ALA photodynamic therapy treatment (RR: 1.07, 95% CI 1.02–1.12, $p = 0.01$; $I^2 = 72\%$) (Fig. 2A). Two trials were identified reporting participant complete clearance rates at 3 months. Photodynamic therapy in combination with BF-200 ALA showed significant higher participant complete clearance rates compared to photodynamic therapy plus MAL (RR: 1.09, 95% CI 1.06–1.12, $p < 0.00001$; $I^2 = 0\%$) (Fig. 2B). However, this difference was not statistically significant at 12 months (RR: 1.10, 95% CI 0.99–1.23, $p = 0.07$; $I^2 = 68\%$) (Fig. 2C).

3.4. Subgroup analysis

Two trials were enrolled in subgroup analysis. BF-200 ALA photodynamic therapy showed higher participant complete clearance rates in comparison to photodynamic therapy plus MAL for the treatment of grade II-III actinic keratosis lesions (RR: 1.24, 95% CI 1.05–1.46, $p = 0.01$; $I^2 = 0\%$). There was no significant difference between BF-200 ALA and MAL when performed in grade I actinic keratosis lesions (RR: 1.15, 95% CI 0.91–1.46, $p = 0.23$; $I^2 = 75\%$) (Fig. 3).

3.5. Recurrence rates

Data on recurrence rates as the number of recurrent lesions was available from two trials. The pooled results showed that lesions treated with BF-200 ALA photodynamic therapy had a significantly lower likelihood for recurrence in comparison to MAL photodynamic therapy at 12 months (RR: 0.67, 95% CI 0.48-0.92, $p = 0.01$; $I^2 = 26\%$) (Fig. 4).

3.6. Adverse events

Data of pain score was available from three trials. Pooled results showed that the combination of photodynamic therapy with BF-200 ALA was perceived as more painful than MAL photodynamic therapy (mean difference: 0.21, 95% CI 0.05-0.37, $p = 0.008$; $I^2 = 6\%$) (Fig. 5A). However, subgroup analysis of pain for face or scalp showed no significant difference between BF-200 ALA and MAL treatment (face mean difference: -0.09, 95%CI -0.57-0.38, $p = 0.70$, $I^2 = 0\%$; scalp mean difference: 0.15, 95%CI -0.12-0.43, $p = 0.27$, $I^2 = 44\%$) (Fig. 5B).

3.7. Bias assessment

All of the included trials had achieved randomization. Only one trial was unclear how the concealment was allocated. Blinding of participants or personnel was performed in 4 of the included trials. Four trials had reported all results for their pre-defined outcomes. Finally, this meta-analysis was at low risk for reporting bias (Fig. 6).

4. Discussion

Photodynamic therapy has been successfully develop to treat dermatological disease since the simplicity of light exposure for the skin and easy accessibility of topical use of photosensitizers. The mechanism of reaction of photodynamic therapy between a photosensitizing compound and a light source is based on the production of reactive oxygen species (ROS). [21] Within the cells of actinic keratosis, the active

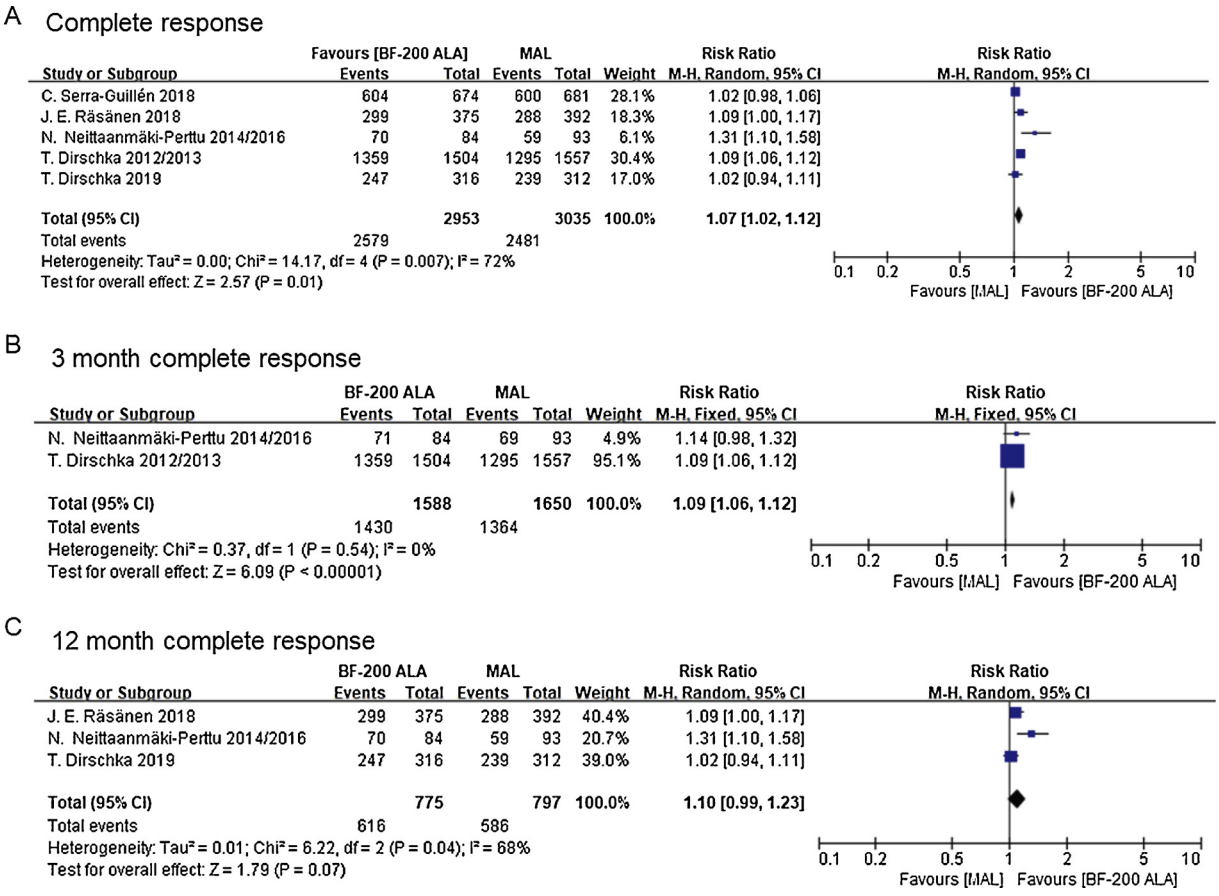

Fig. 2. Forest plots of risk ratios for complete response. (A) Forest plots of risk ratios showed that the complete lesion response rates were significantly higher after BF-200 ALA photodynamic therapy treatment compared with MAL photodynamic therapy; (B) Forest plots of risk ratios showed that photodynamic therapy plus BF-200 ALA had significant higher 3 months participant complete clearance rates; (C) There was not statistically significant difference of complete clearance rates at 12 months between two drugs. BF-200 ALA: 5-aminolevulinic acid nanoemulsion; MAL: methyl-5-aminolevulinate; CI: confidence interval; I^2: index of heterogeneity; M−H: Mantel-Haenszel statistical method; Random: Random effects analysis model; Fix: Fixed effect analysis model.

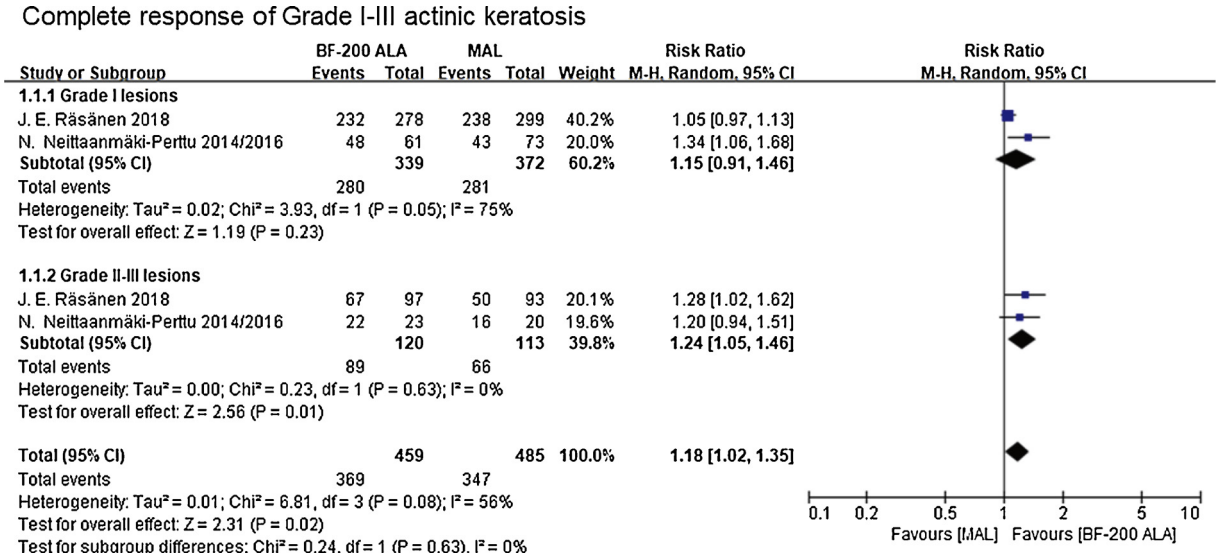

Fig. 3. Forest plots of subgroup analysis of risk ratios for complete response according to the grade of actinic keratosis lesions. Forest plots of risk ratios showed that BF-200 ALA photodynamic therapy had higher participant complete clearance rates for the treatment of grade II-III actinic keratosis lesions, other than grade I actinic keratosis lesions.

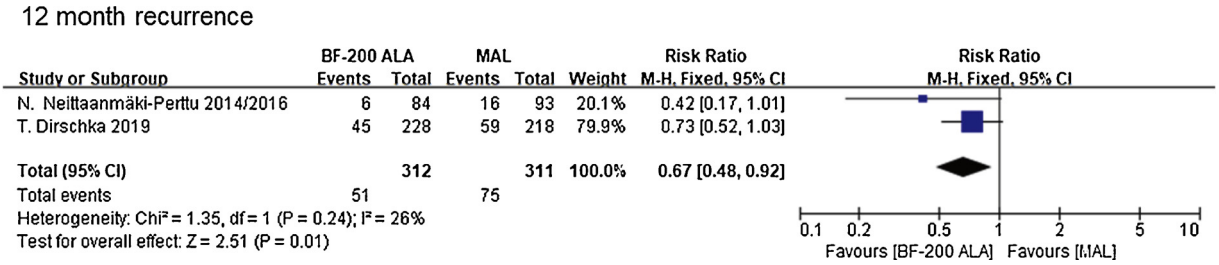

Fig. 4. Forest plots of risk ratios for recurrence at 12 months. Lesions treated with BF-200 ALA photodynamic therapy had significantly lower 12 months recurrence rates.

photosensitizers photoporphyrin IX (PpIX) absorbs light and leads to the generation of ROS thus resulting in damage to cell membranes and lipid peroxidation, induction of cell death [10,22,23].

The first generation photosensitizers for photodynamic therapy treatment are HpD or its purified version Photofrin. However, the prolonged phototoxicities last 6–10 weeks, which limit their use. [24,25] Compared with the first generation photosensitizers, the second generation photosensitizers are pure compounds and have a lower propensity to cause prolonged photosensitivity [26]. Examples are benzoporphyrin derivative monoacid ring A, m-tetrahydroxyphenyl-chlorin, tin ethyl etiopurpurin, phthalocyanies and chlorins. The third generation photosensitizers such as lutetium texaphyrin [27,28] and antibody-conjugated photosensitizers [29] have not yet approved.

ALA and its methl ester MAL are topically applied photosensitizers avoiding the prolonged photosensitivity by systemic administration. MAL was approved in Europe for topical photodynamic therapy of actinic keratosis lesions in 2001 [30,31] and in the USA for the treatment of actinic keratosis in 2004 [32,33]. The application of ALA or MAL dramatically reduced the adverse side effect of prolonged cutaneous phototoxicity. The decreasing of adverse events was attributed to the fully metabolism of endogenous photosensitizer PpIX over 24–48 h [34,35]. However, MAL was withdrawn from the market in the USA because of the similar efficacy of ALA and MAL [36]. Consequent research reported that there was no significant difference between ALA and MAL when it came to complete clearance rates, but MAL caused more pain than ALA during treatment [37].

BF-200 ALA, a nano-emulsified preparation of ALA, increased ALA stability [11] and accelerated the conversion of ALA into PpIX [38]. In healthy volunteer's skin, BF-200 ALA increased PpIX formation in comparison with MAL [39,40]. This improvement in penetration resulted higher complete clearance rates of BF-200 ALA than MAL in grade II-III actinic keratosis [17,18]. In our meta-analysis, BF-200 ALA significantly increased the participants' complete clearance rates compared with MAL at 3 months, but not at 12 months. As described above, we suspected that BF-200 ALA was non-inferior to MAL in the treatment of actinic keratosis. It seems that the use of BF-200 ALA is not necessary.

However, in the subgroup analysis of long-term follow-up researches, the combination of photodynamic therapy with BF-200 ALA was superior to MAL photodynamic therapy in the treatment of grade

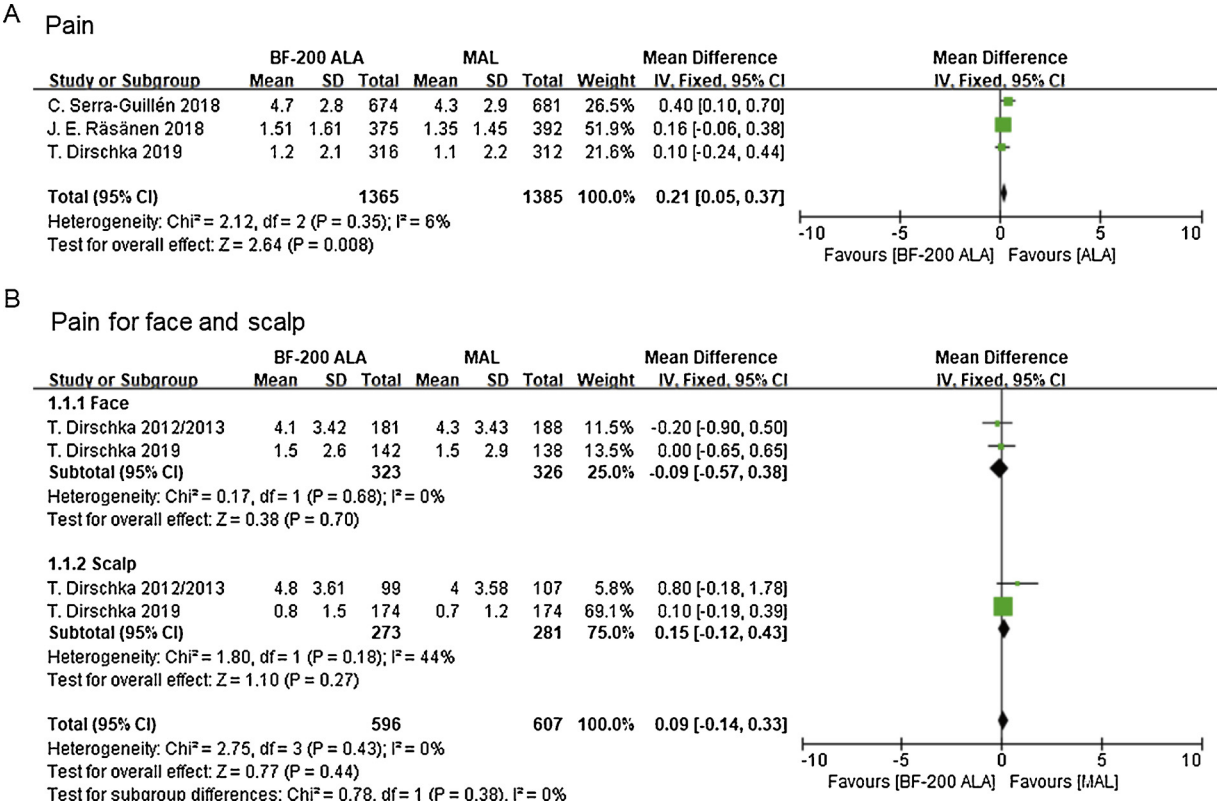

Fig. 5. Forest plots of risk ratios for photodynamic therapy related pain. (A) Forest plots comparing the influences of BF-200 ALA and MAL on pain scores, showed that photodynamic therapy plus BF-200 ALA caused more painful than MAL photodynamic therapy; (B) Subgroup analysis on pain scores according to the location of actinic keratosis lesions, showed no significant difference between two drugs. IV: Inverse Variance statistical method.

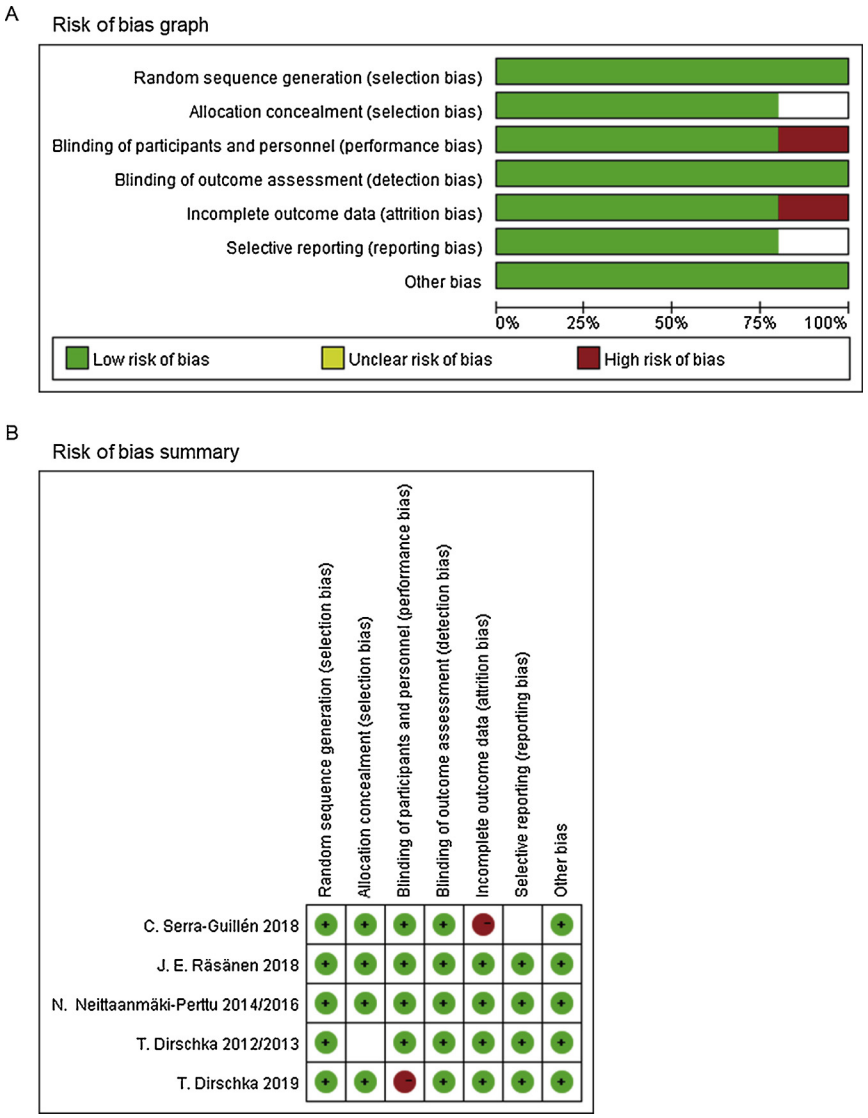

Fig. 6. Risk of bias. (A) Summary of the evaluation of the included randomized controlled trials for each risk of bias item. Review authors' judgments about each risk of bias item presented as percentages across all included clinical trials; (B) Risk of bias evaluation for each included trials. The review authors' judgments on each risk of bias item for each include trials: low risk = '+', high risk = '-', unclear risk of bias = '?'.

II-III lesions. Moreover, 12 months after photodynamic treatment, BF-200 ALA showed less recurrence rates compared with MAL. Thus, we considered significant superiority of BF-200 ALA over MAL.

Although photodynamic therapy with BF-200 ALA could achieve higher efficacy for actinic keratosis, management of treatment-related pain/adverse side effects might be a challenge. The efficacy was associated with elevated pain and local skin reactions. Consistently, our results showed that BF-200 ALA significantly increased the pain score compared with MAL. Since pain intensity is associated with light intensity, narrow-spectrum devices cause more severe pain. The red light source, Aktilite CL 128, could provide a narrow spectrum around 630 nm, which explained the significant difference in pain evaluation analysis. However, in the subgroup analysis of pain score, there was no significant difference between BF-200 ALA and MAL in the treatment of for face or scalp lesions. In the included trials, nevertheless, both narrow and broader light sources were contained. The discrepant results might be attributed to the treatment area size which was a well-known predictor of photodynamic therapy pain. [41]

Additionally, the economic impact of the disease and real incurred costs are needed to be evaluated. A previous meta-analysis indicated that MAL photodynamic therapy was an effective treatment with a favorable value for money profile and daylight photodynamic therapy remained the least expensive option per lesion clears. [42] The clinical trial conducted by J. E. Räsänen studied the cost-effectiveness of photodynamic therapy combined with BF-200 ALA/MAL and showed the costs were similar for both photosensitizer [14]. Another study in our meta-analysis suggested that a 0.25 mm layer of the photosensitizer precursor may lead to lower costs [15]. Whereas, the prices of BF-200 ALA and MAL vary among countries which may lead to actual differences in cost-effectiveness, further researches are warranted to confirm clearer results.

There were several limitations involved in our meta-analysis. Both intra-individual and inter-individual studies were selected in the analysis. The incubation time varied from 0.5 to 3 h. Moreover, light source, exposure time, and length of follow-up were variety. Conclusions regarding the adverse event were contradictory, because of the lacking trials with comparable study variables. Cosmetic outcome comparison data was insufficient. The cost of topical treatments for actinic keratosis was not evaluated.

Altogether, our analysis provided a rationale that the combination of photodynamic therapy with BF-200 ALA offered efficacy benefits compared to photodynamic therapy with MAL for the treatment of

grade II-III actinic keratosis lesion.

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References

[1] A. Dodds, A. Chia, S. Shumack, Actinic keratosis: rationale and management, Dermatol. Ther. 4 (1) (2014) 11–31.
[2] V.D. Criscione, M.A. Weinstock, M.F. Naylor, C. Luque, M.J. Eide, S.F. Bingham, G. Department of veteran affairs topical tretinoin chemoprevention trial, actinic keratoses: natural history and risk of malignant transformation in the veterans affairs topical tretinoin chemoprevention trial, Cancer 115 (11) (2009) 2523–2530.
[3] B. Dreno, J.M. Amici, N. Basset-Seguin, B. Cribier, J.P. Claudel, M.A. Richard, Akteam, Management of actinic keratosis: a practical report and treatment algorithm from AKTeam expert clinicians, J. Eur. Acad. Dermatol. Venereol. 28 (9) (2014) 1141–1149.
[4] N. Jetter, N. Chandan, S. Wang, M. Tsoukas, Field cancerization therapies for management of actinic keratosis: a narrative review, Am. J. Clin. Dermatol. 19 (4) (2018) 543–557.
[5] C.A. Morton, R.M. Szeimies, A. Sidoroff, L.R. Braathen, European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma, J. Eur. Acad. Dermatol. Venereol. 27 (5) (2013) 536–544.
[6] G. Patel, A.W. Armstrong, D.B. Eisen, Efficacy of photodynamic therapy vs other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis, JAMA Dermatol. 150 (12) (2014) 1281–1288.
[7] J.C. Kennedy, R.H. Pottier, D.C. Pross, Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience, Journal of photochemistry and photobiology, B, Biology 6 (1-2) (1990) 143–148.
[8] S. Vegter, K. Tolley, A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe, PLoS One 9 (6) (2014) e96829.
[9] A.K. Gupta, M. Paquet, E. Villanueva, W. Brintnell, Interventions for actinic keratoses, Cochrane Database Syst. Rev. 12 (2012) CD004415.
[10] B. Zhao, Y.Y. He, Recent advances in the prevention and treatment of skin cancer using photodynamic therapy, Expert Rev. Anticancer Ther. 10 (11) (2010) 1797–1809.
[11] T. Maisch, F. Santarelli, S. Schreml, P. Babilas, R.M. Szeimies, Fluorescence induction of protoporphyrin IX by a new 5-aminolevulinic acid nanoemulsion used for photodynamic therapy in a full-thickness ex vivo skin model, Exp. Dermatol. 19 (8) (2010) e302–5.
[12] R.M. Szeimies, P. Radny, M. Sebastian, F. Borrosch, T. Dirschka, G. Krahn-Senftleben, K. Reich, G. Pabst, D. Voss, M. Foguet, R. Gahlmann, H. Lubbert, U. Reinhold, Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study, Br. J. Dermatol. 163 (2) (2010) 386–394.
[13] C. Serra-Guillen, E. Nagore, E. Bancalari, S. Kindem, O. Sanmartin, B. Llombart, C. Requena, I. Serra-Guillen, L. Calomarde, A. Diago, E. Bernia, C. Guillen, A randomized intraindividual comparative study of methyl-5-aminolaevulinate vs. 5-aminolaevulinic acid nanoemulsion (BF-200 ALA) in photodynamic therapy for actinic keratosis of the face and scalp, Br. J. Dermatol. 179 (6) (2018) 1410–1411.
[14] J.E. Rasanen, N. Neittaanmaki, L. Ylitalo, J. Hagman, P. Rissanen, L. Ylianttila, M. Salmivuori, E. Snellman, M. Gronroos, 5-aminolaevulinic acid nanoemulsion is more effective than methyl-5-aminolaevulinate in daylight photodynamic therapy for actinic keratosis: a nonsponsored randomized double-blind multicentre trial, Br. J. Dermatol. (2018).
[15] N. Neittaanmaki-Perttu, T.T. Karppinen, M. Gronroos, T.T. Tani, E. Snellman, Daylight photodynamic therapy for actinic keratoses: a randomized double-blinded nonsponsored prospective study comparing 5-aminolaevulinic acid nanoemulsion (BF-200) with methyl-5-aminolaevulinate, Br. J. Dermatol. 171 (5) (2014) 1172–1180.
[16] N. Neittaanmaki-Perttu, M. Gronroos, T. Tani, E. Snellman, Long-term outcome of daylight photodynamic therapy with Amino-5-laevulinate nanoemulsion vs. Methyl-5-aminolaevulinate for actinic keratoses, Acta Derm. Venereol. 96 (5) (2016) 712–713.
[17] T. Dirschka, P. Radny, R. Dominicus, H. Mensing, H. Bruning, L. Jenne, L. Karl, M. Sebastian, C. Oster-Schmidt, W. Klovekorn, U. Reinhold, M. Tanner, D. Grone, M. Deichmann, M. Simon, F. Hubinger, G. Hofbauer, G. Krahn-Senftleben, F. Borrosch, K. Reich, C. Berking, P. Wolf, P. Lehmann, M. Moers-Carpi, H. Honigsmann, K. Wernicke-Panten, C. Helwig, M. Foguet, B. Schmitz, H. Lubbert, R.M. Szeimies, A.-C.S. Group, Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo, Br. J. Dermatol. 166 (1) (2012) 137–146.
[18] T. Dirschka, P. Radny, R. Dominicus, H. Mensing, H. Bruning, L. Jenne, L. Karl, M. Sebastian, C. Oster-Schmidt, W. Klovekorn, U. Reinhold, M. Tanner, D. Grone, M. Deichmann, M. Simon, F. Hubinger, G. Hofbauer, G. Krahn-Senftleben, F. Borrosch, K. Reich, C. Berking, P. Wolf, P. Lehmann, M. Moers-Carpi, H. Honigsmann, K. Wernicke-Panten, S. Hahn, G. Pabst, D. Voss, M. Foguet, B. Schmitz, H. Lubbert, R.M. Szeimies, A.-C.S. Group, Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis, Br. J. Dermatol. 168 (4) (2013) 825–836.
[19] T. Dirschka, S. Ekanayake-Bohlig, R. Dominicus, R. Aschoff, E. Herrera-Ceballos, R. Botella-Estrada, A. Hunfeld, M. Kremser, B. Schmitz, H. Lubbert, S. Puig, A randomized, intraindividual, non-inferiority, Phase III study comparing daylight photodynamic therapy with BF-200 ALA gel and MAL cream for the treatment of actinic keratosis, J. Eur. Acad. Dermatol. Venereol. 33 (2) (2019) 288–297.
[20] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement, Open Med. 3 (3) (2009) e123–30.
[21] A.D. Garg, D. Nowis, J. Golab, P. Agostinis, Photodynamic therapy: illuminating the road from cell death towards anti-tumour immunity, Apoptosis 15 (9) (2010) 1050–1071.
[22] P. Agostinis, K. Berg, K.A. Cengel, T.H. Foster, A.W. Girotti, S.O. Gollnick, S.M. Hahn, M.R. Hamblin, A. Juzeniene, D. Kessel, M. Korbelik, J. Moan, P. Mroz, D. Nowis, J. Piette, B.C. Wilson, J. Golab, Photodynamic therapy of cancer: an update, CA Cancer J. Clin. 61 (4) (2011) 250–281.
[23] J.M. Spencer, C. Hazan, S.H. Hsiung, P. Robins, Therapeutic decision making in the therapy of actinic keratoses, J. Drugs Dermatol. 4 (3) (2005) 296–301.
[24] G. Dragieva, L. Scharer, R. Dummer, W. Kempf, Photodynamic therapy–a new treatment option for epithelial malignancies of the skin, Onkologie 27 (4) (2004) 407–411.
[25] C. Fritsch, G. Goerz, T. Ruzicka, Photodynamic therapy in dermatology, Arch. Dermatol. 134 (2) (1998) 207–214.
[26] J. Moan, K. Berg, Photochemotherapy of cancer: experimental research, Photochem. Photobiol. 55 (6) (1992) 931–948.
[27] S.W. Young, K.W. Woodburn, M. Wright, T.D. Mody, Q. Fan, J.L. Sessler, W.C. Dow, R.A. Miller, Lutetium texaphyrin (PCI-0123): a near-infrared, water-soluble photosensitizer, Photochem. Photobiol. 63 (6) (1996) 892–897.
[28] K.W. Woodburn, Q. Fan, D. Kessel, Y. Luo, S.W. Young, Photodynamic therapy of B16F10 murine melanoma with lutetium texaphyrin, J. Invest. Dermatol. 110 (5) (1998) 746–751.
[29] L.B. Josefsen, R.W. Boyle, Photodynamic therapy: novel third-generation photosensitizers one step closer? Br. J. Pharmacol. 154 (1) (2008) 1–3.
[30] C.A. Morton, Methyl aminolevulinate (Metvix) photodynamic therapy - practical pearls, J. Dermatolog. Treat. 14 (Suppl 3) (2003) 23–26.
[31] C.A. Morton, S.B. Brown, S. Collins, S. Ibbotson, H. Jenkinson, H. Kurwa, K. Langmack, K. McKenna, H. Moseley, A.D. Pearse, M. Stringer, D.K. Taylor, G. Wong, L.E. Rhodes, Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group, Br. J. Dermatol. 146 (4) (2002) 552–567.
[32] N.C. Zeitouni, A.R. Oseroff, S. Shieh, Photodynamic therapy for nonmelanoma skin cancers, Current review and update, Molecular immunology 39 (2003) 17–18 1133-6.
[33] J. Garcia-Zuazaga, K.D. Cooper, E.D. Baron, Photodynamic therapy in dermatology: current concepts in the treatment of skin cancer, Expert Rev. Anticancer Ther. 5 (5) (2005) 791–800.
[34] J.E. Blume, A.R. Oseroff, Aminolevulinic acid photodynamic therapy for skin cancers, Dermatol. Clin. 25 (1) (2007) 5–14.
[35] C.A. Morton, Photodynamic therapy for nonmelanoma skin cancer–and more? Arch. Dermatol. 140 (1) (2004) 116–120.
[36] F.J. Moloney, P. Collins, Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis, Br. J. Dermatol. 157 (1) (2007) 87–91.
[37] C. Housset, O. Boucher, P.M. Girard, J. Leibowitch, A.G. Saimot, C. Brechot, C. Marche, Immunohistochemical evidence for human immunodeficiency virus-1 infection of liver Kupffer cells, Hum. Pathol. 21 (4) (1990) 404–408.
[38] R. Schulten, B. Novak, B. Schmitz, H. Lubbert, Comparison of the uptake of 5-aminolevulinic acid and its methyl ester in keratinocytes and skin, Naunyn Schmiedebergs Arch. Pharmacol. 385 (10) (2012) 969–979.
[39] S. McMain, C.D. Webster, R.J. Menzies, The post-assessment careers of mentally disordered offenders, Int. J. Law Psychiatry 12 (2-3) (1989) 189–201.
[40] C.V. Nissen, S.R. Wiegell, P.A. Philipsen, H.C. Wulf, Short-term chemical pretreatment cannot replace curettage in photodynamic therapy, Photodermatology, photoimmunology & photomedicine 32 (3) (2016) 146–152.
[41] C.B. Warren, L.J. Karai, A. Vidimos, E.V. Maytin, Pain associated with aminolevulinic acid-photodynamic therapy of skin disease, J. Am. Acad. Dermatol. 61 (6) (2009) 1033–1043.
[42] P. Calzavara-Pinton, C. Zane, M. Arisi, P.A. Hamon, N.T. Tanova, Evaluation of the costs of topical treatments for actinic keratosis based on lesion response and the affected area, Giornale italiano di dermatologia e venereologia : organo ufficiale, Soc. Ital. Dermatol. Sifilogr. Sezioni Interprov. Soc. Ital. Dermatol. Sifilogr. 153 (6) (2018) 764–775.