Manuscript category: Original article

Chemical peelings for the treatment of actinic keratosis: A systematic review and meta-analysis

Running head: Chemical peelings for actinic keratosis

Theresa Steeb[1], Elias A.T. Koch[1], Anja Wessely[1], Luitgard G. Wiest[2], Lutz Schmitz[3,4], Carola Berking[1], Markus V. Heppt[1,*]

[1] Department of Dermatology, Universitätsklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany

[2] Private practice of Dermatology, Munich, Germany

[3] Department of Dermatology, Venereology and Allergology, Ruhr-University, Bochum, Germany

[4] Institute of Dermatopathology, MVZ Corius DermPathBonn, Bonn, Germany

* Corresponding Author
Markus V. Heppt, MD, MSc, MHBA
Department of Dermatology
University Hospital Erlangen
Friedrich-Alexander University Erlangen-Nürnberg
Ulmenweg 18
91054 Erlangen, Germany
Phone: 0049-9131-85-35747
E-Mail: markus.heppt@uk-erlangen.de

Manuscript word count

Body:	**2761**
Abstract:	**300**
Figures:	3
Tables:	2 (regular), 1 Supplementary
Supporting information:	PRISMA Checklist

Funding: none.

Conflicts of Interest: CB has been member of advisory boards for Almirall Hermal, Biofrontera, Galderma, and Leo Pharma. CB has received speaker´s honoraria by Almirall Hermal, Galderma, and Leo Pharma. CB has received funding for clinical research by Leo Pharma. MVH has received honoraria by Galderma, Almirall Hermal and Sanofi. LS has received speaker´s honoraria by Almirall Hermal, Biofrontera, Galderma, Mylan and Sanofi. LS has been member of advisory boards for Almirall Hermal. The remaining authors declare no conflicts of interests.

Abstract

Background: Actinic keratosis (AK) is a common precancerous lesion of the skin that may be treated with chemical peelings. Despite their long-standing usage and clinical experience, no evidence-based recommendation regarding the efficacy and safety of chemical peelings for AK exists.

Objectives: To systematically review and synthesize the current knowledge on chemically exfoliative peelings as interventions for AK.

Methods: We performed a systematic literature research in Medline, Embase, and CENTRAL and hand-searched pertinent trial registers for eligible records until 5 August 2019. Results from individual studies were pooled using a random-effects model or described in a qualitative synthesis. The risk of bias was estimated with the tools provided by the Cochrane Collaboration (randomized and non-randomized trials) and the Evidence Project (single-arm trials).

Results: Four randomized controlled trials, 2 non-randomized controlled trials and 2 single-arm studies with a total sample size of n=170 patients were included. Trichloroacetic acid (TCA) plus Jessner's solution showed significantly lower participant complete clearance (RR 0.36, 95% CI 0.14-0.90, 2 studies, I^2=0%, p=0.03) and lower lesion clearance (RR 0.92, 95% CI 0.85-0.99, 1 study, p=0.03) compared to 5-fluorouracil (5-FU) 5% cream. TCA as monotherapy showed lower lesion complete clearance (RR 0.75, 95% CI 0.69-0.82, 2 studies, I^2=7%, p<0.001) and lower mean lesion reduction per patient compared to conventional photodynamic therapy

(cPDT) (MD -20.48, 95% CI -31.55 to -9.41, 2 studies, I^2=43%, p=0.0003). Pain was more pronounced in patients treated with cPDT in comparison to TCA (MD -1.71 95% CI -3.02 to -0.41, 2 studies, I^2=55%, p=0.01). In the single arm studies, 5-FU plus glycolic acid showed 92% lesion clearance and phenol peeling 90.6% participant complete clearance. All studies showed a high risk for bias.

Conclusions: Future high-quality studies and a standardization of peeling protocols are warranted to determine the value of chemical peelings in the treatment of AK.

Keywords: actinic keratosis; chemical peelings; trichloroacetic acid; Jessner's solution, glycolic acid; chemical peeling; salicylic acid

Background

Lifelong exposure to ultraviolet (UV) radiation can lead to the development of actinic keratosis (AK).[1,2] They represent common skin lesions due to a prevalence of up to 60% in light-skinned individuals aging 60 years or older. AK can progress into invasive squamous cell carcinoma of the skin (cSCC), although the conversion risk for an individual lesion is estimated low.[3] However, if multiple lesions or clinical signs of field cancerization are present, the progression rates increase markedly, and spontaneous regression is less likely to occur. International guidelines recommend early and consequent treatment of AK as it is clinically and histologically difficult to predict if and which lesions will progress into cSCC.[4,5] The concept of field cancerization has initiated a paradigm shift in AK therapy from lesion-directed to field-directed therapies. While lesion-specific methods such as cryosurgery and laser ablation offer a fast and easy approach for isolated lesions, field-directed treatments are preferable for multiple AK as they also address subclinical changes of an actinically damaged field. Numerous effective and safe interventions are available for the treatment of AK. Thus, selecting an appropriate therapy may pose a major challenge in daily practice and a framework for evidence-based decision-making is urgently needed for this dermatologic condition.

Chemical peelings are classically used for skin rejuvenation by improving and smoothing the skin texture. They mediate unspecific chemical ablation of skin layers to a certain depth, followed by regeneration of the epidermis and superficial dermis.[6] Chemically exfoliative peelings are normally safe procedures when performed by qualified, experienced practitioners. However, some unpredictability of the procedure and risks such as infection and scarring are possible and may occur, albeit infrequently. In patients with AK, chemical peelings can be applied to large skin areas and are considered for the treatment of multiple or clustered lesions and field cancerization. Despite their long-standing usage in clinical practice, no evidence-based recommendation regarding the efficacy and safety chemical peelings for AK exists. Hence, the aim of this study was to perform a systematic review and meta-analysis of chemical peelings as intervention for AK.

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 (CRD2019146403). This protocol was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7] and the Cochrane Handbook for Systematic Reviews.[8]

Eligibility criteria

We included adult patients (≥18 years of age) with a clinical or histopathological diagnosis of AK. Both immunosuppressed and immunocompetent individuals were eligible. Patients were to be treated with any chemical peeling, including one of the following solutions: Jessner's solution, glycolic acid, trichloroacetic acid (TCA), salicylic acid or any other chemically exfoliative peeling, regardless of the respective concentration used. Sequential or combination approaches with other treatments, such as topical interventions, were allowed. Since we wanted to include all available evidence, we included prospective inter-individual or intra-individual studies as well as retrospective studies. Besides, case series with n>5 patients were included. No language restrictions were set.

Types of outcome measures

The primary outcomes were the following efficacy endpoints: (i) participant complete clearance, defined as the rate of participants who had all (100%) baseline lesions cleared (dichotomous outcome); (ii) lesion-specific clearance, measured as the number of cleared lesions after end of treatment compared to baseline (dichotomous outcome), and (iii) mean lesion reduction rate per patient (continuous outcome). The secondary outcomes were: (iv) treatment-related pain, reported on a visual analogue scale (VAS) from 0 (none) to 10 (extreme pain) as measure of tolerability (continuous outcome), and (v) occurrence of treatment-induced scarring as a proxy of cosmesis (dichotomous outcome).

Search methods for identification of studies

We searched the electronic databases Medline, Embase (both via Ovid) and the Cochrane library CENTRAL until 5 August 2019 to identify all relevant records. The

search strategies can be obtained from the Supplementary. 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/), EU Clinical Trials Register (www.clinicaltrialsregister.eu/). For ongoing trials and completed trials without data publication, principal investigators or trial sponsors have been contacted to obtain preliminary or unpublished data. Besides, reference lists of included records were screened as well.

Selection of studies

Two authors (TS, EATK) independently screened titles and abstracts for eligibility that were identified in the electronic database searches and trial registers. For records that were considered relevant according to title and abstract screening, full-text articles were obtained, and inclusion and exclusion criteria were applied. Whenever discrepancies arose, resolution was be achieved by discussion with a third independent author (MVH).

Data extraction and management

Information for each included study regarding design, baseline characteristics, intervention, outcomes and risk of bias were collected and summarized by two authors independently (TS, EATK) using Microsoft Excel 2010 and Review Manager Version 5.3.[9] Wherever possible and suitable, we performed a pairwise, i.e. comparison-specific meta-analysis of quantitative data using Review Manager 5.3.[9] We used a random-effects model as clinical and methodological heterogeneity between the studies was likely. 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. For the intervention conventional photodynamic therapy (PDT), we did not distinguish between aminolevulinate (ALA) and methyl-aminolevulinate (MAL) as photosensitizers and pooled them as the efficacy data for both photosensitizers has been widely concordant in previous RCTs.[10,11] If meta-analysis for an outcome was not possible, we described the results qualitatively.

Assessment of Risk of Bias and the Certainty of the Body of Evidence

The risk of bias of the studies was assessed independently by two authors (TS, EK). Three different tools to assess the methodological quality and the risk of bias of the included studies were selected: (i) Cochrane risk of bias tool for the evaluation of RCTs[12]; (ii) Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies[13]; (iii) quality assessment tool for before-after (pre-post) studies with no control group as described by the Evidence Project group for uncontrolled before-after studies.[14] Discrepancies were thoroughly discussed and resolved with the full texts and supplementary material. If at least 10 records reported a specific comparison, we intended to assess publication bias by creating a funnel plot.[8]

Results

Study identification

Our initial literature search identified 3,299 references (last updated 05 August 2019). After removing duplicates, 2,774 citations remained. Following title and abstract screening, 2,731 studies were not considered relevant since they did not meet our inclusion criteria and were consequently excluded. Hence, 43 records underwent full text review (Fig. 1). The majority of these 43 records was excluded either because data or the outcome was unclearly reported or because the study design did not match our eligibility criteria (n=11 each). Additionally, no AK were investigated in 5 studies which were consequently dismissed. In another 5 studies, the sample size was n<5 and was therefore considered ineligible for our review. Furthermore, 2 studies investigated the wrong intervention and one study was a long-term analysis of an included study and did not provide any additional data.[15] Hence, 8 studies with an overall sample size of n=170 (range 13-32) were included in our systematic review (Table 1).[16-23] The studies were published between 1995 and 2018 and were 4 RCTs, 2 non-randomized controlled trials and 2 single-arm studies.

Two studies investigated a combination of TCA 35% peeling in combination with Jessner's solution in comparison to 5-fluorouracil (5-FU) 5% cream for AKs located on the face.[16,20] Another two studies compared TCA 50% peeling to conventional PDT with MAL for AKs on the scalp[17] and 35% TCA peeling to conventional PDT with ALA for AKs located on the face, scalp, extremities and the trunk, respectively.[18] One study assessed 70% glycolic acid in combination with 5% 5-FU solution compared to glycolic

acid monotherapy for AKs on the face[21] and another one compared tretinoin 5% peeling to tretinoin 0.5% cream for AKs on the forearms.[23] The single arm studies prospectively examined patients with AKs on the face, scalp, extremities or trunk treated with 100% pure phenol[19] or with 5-FU 5% followed by chemical peeling with glycolic acid[22] in patients with AK in the head and neck area, respectively.

Outcomes of interest

Participant complete clearance

TCA 35% and Jessner's solution showed significantly lower participant complete clearance compared to 5-FU 5% cream (RR 0.36, 95% CI 0.14-0.90, 2 studies, I^2=0%, p=0.03) (Fig. 2a)[16,20]. 5-FU in combination with 70% glycolic acid was not significantly more effective in achieving a participant complete clearance than 70% glycolic acid alone[21] (Table 2). Nor was there a significant difference regarding this outcome between 50% TCA and MAL-PDT.[17] Additionally, the participant complete clearance rate was reported as 30% (6/20) for the intervention 5-FU in combination with 70% glycolic acid[22] and 90.6% (29/32) for 100% phenol peeling.[19]

Lesion complete clearance

Data on lesion complete clearance was available from 2 studies comparing TCA to conventional PDT.[17,18] TCA demonstrated significantly lower lesion complete clearance than conventional PDT (RR 0.75, 95% CI 0.69-0.82, I^2=7%, 2 studies, p<0.001 (Fig. 2b). 35% TCA and Jessner's solution achieved lower clearance in comparison to 5-FU (RR 0.92, 95% CI 0.85-0.99, 1 study, p=0.03).[20] The combination of 5-FU 5% and 70% glycolic acid showed a significantly higher lesion complete clearance rate than 70% glycolic acid monotherapy (RR 5.87, 95% CI 4.39-7.85, 1 study, p<0.001).[21] Additional data from the single-arm study investigating 5-FU plus 70% glycolic acid reported a lesion clearance rate of 92% (322/350).[22]

Mean lesion reduction per patient

TCA showed significantly lower mean lesion reduction rates per patient in comparison to conventional PDT (MD -20.48, 95% CI -31.55 to -9.41, I^2=43%, 2 studies, p=0.0003) (Fig. 2c).[17,18] No significant difference was observed for 35% TCA in combination with Jessner's solution versus 5-FU 5% cream.[20] The combination of 5-FU and 70% glycolic acid was significantly more effective than 70% glycolic acid monotherapy (MD 74.70, 95% CI 69.95-79.45, 1 study, p<0.0001).[21]

Scarring

The number of patients who developed scars due to treatment was only reported in 2 studies.[18,20] In the study comparing TCA and Jessner's solution to 5-FU 5% cream, scarring occurred in none of the patients.[20] In the study comparing TCA to conventional ALA-PDT, 21.4% (6/28) of the patients reported scarring on the site treated with TCA, whereas scarring did not occur in the sites treated with ALA-PDT.[18]

Pain

Pain was reported on the VAS in 2 studies comparing TCA peeling to conventional PDT.[17,18] Pain was more pronounced in patients who were treated with PDT in comparison to TCA (MD -1.71, 95% CI -3.02 to -0.41, I^2= 55%, 2 studies, p=0.01) (Fig. 2d).

Risk of bias assessment

As less than 10 studies investigated a specific comparison, we did not create a funnel plot to assess publication bias. Overall, the majority of the 4 RCTs were at high risk for selection bias as only one study clearly described the generation of a random sequence generation and performed concealment of the allocation (Fig. 3, left panel). Blinding of the participant was performed in none of the studies, whereas blinding of the outcome assessor was explicitly described in one of the studies. Besides, the studies showed an unclear to low attrition bias. However, they were at unclear to high risk for selective reporting and 2 studies were at increased risk for other bias as they only included either female or male participants. The two non-randomized studies were at risk for selection bias and confounding. However, classification of interventions was similar in the intervention and control groups and there were no deviations from the intended interventions. There was a moderate risk for missing data in one study and a serious risk for a biased measurement of outcomes and selective reporting in both studies (Fig. 3, middle panel). The two single-arm studies were at an increased risk for bias as well, mainly since they did not report both pre- and post-intervention data (Fig. 3, right panel).

Discussion

Chemically exfoliative peelings have been used in dermatological practice for various indications over decades. In addition to skin rejuvenation, peelings have been consistently deployed in the treatment of AK as an ablative approach. Surprisingly,

current treatment guidelines fall short of providing specific recommendations for the treatment of AK with chemical peelings.[5] This may be due to the fact that the evidence for chemical peelings appears limited compared to other topical interventions. In this study, we included 8 studies with a total sample size of only 170 patients, although we followed a broad literature search, also covering trial registers and grey literature. Furthermore, we did not limit the study design to RCTs but also included non-randomized interventional trials and uncontrolled before-after studies. These results highlight that the evidence for chemical peelings is limited regarding the quantitative amount of published data and records compared to other topical drugs.

Methodologically, the data analysis and interpretation of the results was challenged by the presence of multiple study designs and the investigation of multiple distinct comparisons. Two studies investigated TCA plus Jessner's solution versus conventional PDT and TCA versus 5-FU, respectively. For both comparisons we calculated pooled estimates with a random-effects model revealing that the TCA-mediated peelings were consistently significantly inferior regarding the efficacy outcomes of interest. Furthermore, scarring was observed in one study in 21.4% of patients treated with TCA but not in those treated with PDT, suggesting that the risk-benefit ratio of peelings may indeed be unfavourable. Nevertheless, relatively high lesion and participant clearance rates were observed in the single-arm studies investigating the combination of 5-FU plus glycolic acid (92%) and phenol peeling (90.6%). The latter substance mediates chemical ablation affecting the epidermis to the deeper reticular dermis, while TCA 35% with or without Jessner's solution achieves chemexfoliation of medium depth involving epidermis and papillary dermis. Thus, these observations may indicate that deep depth peelings may be favourable over medium depth peelings regarding lesion clearance, although the level of ablation increases the risk for scarring and is usually accompanied by a prolonged downtime due to post-interventional wound healing. Nevertheless, the high lesion clearance rates achieved with deep peelings supports the hotly debated hypothesis that the stroma and mesenchymal component located below the epidermal lesions critically contribute to the maintenance and potentially progression of AK.[24] Regarding pain, data was only available for studies investigating conventional PDT, as painful sensation is commonly associated with this treatment modality. Patients experienced significantly more pain on the side treated with PDT than on the side treated with TCA.

These results are consistent with other studies investigating pain in patients who had undergone conventional PDT.[25,26]

We are aware that the conclusions which can be drawn from the meta-analyses and the included primary studies are limited and should be interpreted with caution. The primary studies were judged as at high risk for bias and of rather poor methodologic quality, regardless of their study design. Most importantly, neither the participants were blinded in the trials nor were sham interventions performed in any of the controlled studies, although this would have substantially improved the credibility of the results. Besides, the studies had sample sizes ranging from 13 to 32 participants. Two studies only included men[17,20] and one only women.[23] Including only one sex in a small sample size introduces high risk for selection bias. These factors contribute to an overall low certainty of evidence for the outcomes investigated in this meta-analysis. A further limitation comes from the selection of the outcomes. The efficacy endpoints which were chosen here refer to short-term clearance rates but may not be able to entirely reflect the long-term results, most importantly the prevention of cSCC over a longer period of time. Pain and scarring were investigated as proxies for tolerability and cosmesis, respectively. In particular, the cosmetic outcome is multi-faceted and hard to evaluate based on objective parameters. Furthermore, the application of the peelings was not performed in a standardized fashion. The concentration of the peelings used varied across the studies, for example some studies investigate 35% TCA while others evaluated 50% TCA. Besides, the mode of application (e.g. cotton-tipped applicators vs. sterile gauze) can also bias the outcome and is often chosen according to the practitioner's preference. Hence, standardized protocols are urgently needed. Altogether, we present an up-to-date and comprehensive analysis to guide the use of chemical peelings for the treatment of AK, both for clinical practice and future guideline recommendations. We conclude that future high-quality studies as well as harmonizing and standardizing peeling protocols are necessary to determine the value of chemical peelings in the treatment of AK.

Acknowledgements

None.

References

1 Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42**: 4-7.

2 Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42**: 8-10.

3 Criscione VD, Weinstock MA, Naylor MF *et al.* Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer* 2009; **115**: 2523-30.

4 de Berker D, McGregor JM, Mohd Mustapa MF *et al.* British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol* 2017; **176**: 20-43.

5 Heppt MV, Leiter U, Steeb T *et al.* S3 guideline for actinic keratosis and cutaneous squamous cell carcinoma - short version, part 1: diagnosis, interventions for actinic keratoses, care structures and quality-of-care indicators. *J Dtsch Dermatol Ges* 2020; **18**: 275-94.

6 Fischer TC, Perosino E, Poli F *et al.* Chemical peels in aesthetic dermatology: An update 2009. *J Eur Acad Dermatol Venereol* 2010; **24**: 281-92.

7 Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009; **3**: e123-30.

8 Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

9 Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre TCC, 2014.

10 Tarstedt M, Gillstedt M, Wennberg Larko AM *et al.* Aminolevulinic acid and methyl aminolevulinate equally effective in topical photodynamic therapy for non-melanoma skin cancers. *J Eur Acad Dermatol Venereol* 2016; **30**: 420-3.

11 Dirschka T, Ekanayake-Bohlig S, Dominicus R *et al.* 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* 2019; **33**:288-97

12 Higgins JP, Altman DG, Gotzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

13 Sterne JA, Hernan MA, Reeves BC *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.

14 Kennedy CE, Fonner VA, Armstrong KA *et al.* The Evidence Project risk of bias tool: assessing study rigor for both randomized and non-randomized intervention studies. *Syst Rev* 2019; **8**: 3.

15 Witheiler DD, Lawrence N, Cox SE *et al.* Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Dermatol Surg* 1997; **23**: 191-6.

16 Alfaro OL, Alcala PD, Navarrete FG *et al.* Effectiveness of Jessner's solution plus 35% trichloroacetic acid versus 5% 5-fluorouracil on multiple facial actinic keratosis. *Dermatol Rev Mex* 2012; **56**: 38-46.

17 Di Nuzzo S, Cortelazzi C, Boccaletti V *et al.* Comparative study of trichloroacetic acid vs. photodynamic therapy with topical 5-aminolevulinic acid for actinic keratosis of the scalp. *Photodermatol Photoimmunol Photomed* 2015; **31**: 233-8.

18 Holzer G, Pinkowicz A, Radakovic S *et al.* Randomized controlled trial comparing 35% trichloroacetic acid peel and 5-aminolaevulinic acid photodynamic therapy for treating multiple actinic keratosis. *Br J Dermatol* 2017; **176**: 1155-61.

19 Kaminaka C, Yamamoto Y, Yonei N *et al.* Phenol peels as a novel therapeutic approach for actinic keratosis and Bowen disease: prospective pilot trial with assessment of clinical, histologic, and immunohistochemical correlations. *J Am Acad Dermatol* 2009; **60**: 615-25.

20 Lawrence N, Cox SE, Cockerell CJ *et al.* A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Arch Dermatol* 1995; **131**: 176-81.

21 Marrero GM, Katz BE. The new fluor-hydroxy pulse peel: A combination of 5-fluorouracil and glycolic acid. *Dermatol Surg* 1998; **24**: 973-8.

22 Sandoval Osses M, Garcia-Huidobro Ramirez I, Molgo Novell M. Safety and effectiveness of the association of 5-fluorouracil and glycolic acid peeling for the treatment of multiple actinic keratoses. *Piel* 2010; **25**: 4-8.

23 Sumita JM, Miot HA, Soares JLM *et al.* Tretinoin (0.05% cream vs. 5% peel) for photoaging and field cancerization of the forearms: randomized, evaluator-blinded, clinical trial. *J Eur Acad Dermatol Venereol* 2018; **32**: 1819-26.

24 Hu B, Castillo E, Harewood L *et al.* Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. *Cell* 2012; **149**: 1207-20.

25 Reinhold U, Dirschka T, Ostendorf R *et al.* A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz(®)) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED(®) lamp. *Br J Dermatol* 2016; **175**; 696-705.

26 Jansen MHE, Kessels J, Nelemans PJ *et al.* Randomized Trial of Four Treatment Approaches for Actinic Keratosis. *N Engl J Med* 2019; **380**: 935-46.

Figure legends

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

Fig. 2: Comparison-specific meta-analysis of interventions. (a) Risk ratio for a participant to have all AK (100%) cleared for the intervention TCA 35% and Jessner's solution in comparison to 5-FU 5% cream. (b) Risk ratio to have AK cleared for the intervention TCA 35% in comparison to conventional PDT. (c) Mean difference in the lesion reduction rate per patient the intervention TCA 35% in comparison to conventional PDT. (d) Mean difference in the outcome pain, measured on a visual analogue scale ranging from 0 to 10 for the intervention TCA 35% in comparison to PDT. In all cases, forest plots with at least 2 RCTs are shown. 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).

Fig. 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study: (left panel) risk of bias evaluation for each RCT; ; (middle panel) risk of bias evaluation for the non-randomized controlled studies; (right panel) risk of bias evaluation for each single-arm study.

Table legends

Table 1: Characteristics of included studies (n=8).

Table 2: Results of the primary and secondary outcomes on chemical peelings for AK investigated in this systematic review.

Supplementary Table S1: Overview on the search strategy in Medline, Embase and the Cochrane Library CENTRAL

Table 1: Characteristics of included studies (n=8).

Study	Design	Intervention	Control	Localization	Sample Size
Alfaro Orozco 2012	Single-centre, intra-individual trial, not randomized	Single application of Jessner's solution and 35% TCA	Application of 5% 5-fluorouracil cream once daily for 6 weeks	Face	20
Di Nuzzo 2015	Single-centre, randomized controlled, intra-individual trial	After treatment with acetone, 50% TCA was applied with sterile gauze until the onset of an evident "frosting"	Application of MAL under occlusion for 3 h, then illumination with a diode light at 37 J/cm^2	Scalp	13, only male participants
Holzer 2016	Single-centre, randomized, controlled, observer-blinded, intra-individual trial	After topical anaesthesia for 30 minutes with a cream containing 5% lidocaine and 5% prilocaine the skin was cleaned with 95% isopropyl alcohol and degreased with acetone soaked sponges. 35% TCA was then applied with cotton buds in several layers to the target area until the appearance of an even pink white frosting.	Application of ALA for 4 h under occlusion, followed by illumination using a dose of 75 J/cm^2 at an irradiance of 75 mW/cm^2	Face, scalp, extremities, trunk	28

Kaminaka 2018	Single-centre, single-arm pilot study	100% pure phenol was locally applied to lesions once a month up to a maximum of 8 months using cotton-tipped applicators until an even white frosting appeared.	none	Face, scalp, extremities, trunk	32
Lawrence 1995	Single-centre, intra-individual trial, not randomized	Application of Jessner's Solution followed by 35% TCA	Application of 5% fluorouracil twice daily for 3 weeks by the patient (right side)	Face	15, only male participants
Marrero 1998	Single-centre, randomized controlled, intra-individual trial	Application of 70% glycolic acid for 2 min., followed by neutralisation with water; after this application of 5% 5-fluorouracil solution	Application of 70% glycolic acid for 2 min., followed by neutralisation with water for 2 min.	Face	18
Sandoval Osses 2009	Single-centre, single-arm study	5-Fluorouracil 5% was applied twice daily for 7 days, followed by chemical peeling with 70% glycolic acid, and finally 7 days of rest, with no therapy	None	Head and neck	20
Sumita 2018	Single-center, prospective, randomized, intra-individual,	Eight sequential applications of 5% tretinoin as peeling every two weeks. The	Tretinoin 0,5% cream three alternate nights a week for 24 weeks	Forearms	24, only female participants

	evaluator-blinded trial	tretinoin peel was removed with soap and water after six hours at home.			

Abbreviations: ALA = 5-aminolevulinate; MAL = methyl 5-aminolevulinate; TCA = trichloroacetic acid.

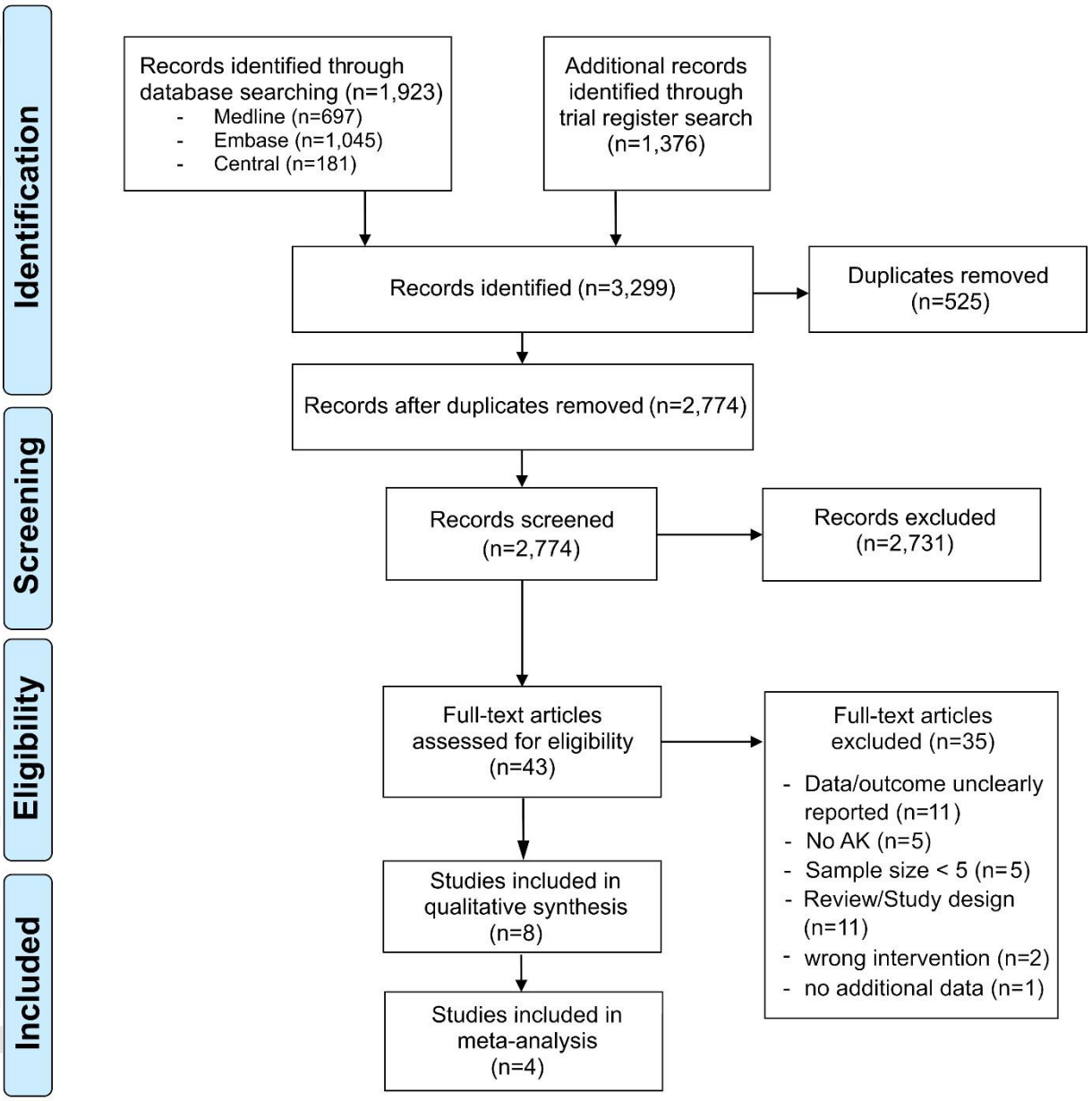
Table 2: Results of the primary and secondary outcomes on chemical peelings for AK investigated in this systematic review.

Comparison		Participant complete clearance	Lesion complete clearance	Mean reduction rate per patient	Pain (VAS)
TCA vs. PDT **2 studies**	Crude rate	0% (0/13) vs. 15.4% (2/13)*	66.1% (80/121) vs. 82.1% (101/123) 60.5% (214/354 vs. 82.6% (317/384)	65.9±12.6 vs. 81.9±12 51.1±28.7 vs. 78.7±26.2	7.31±1.55 vs. 8.38±1.56 5.1±2.6 vs. 7.5±2.3
	Effect estimate	RR 0.20 (95% CI 0.01-3.80)*	RR 0.75 (95% CI 0.69-0.82)	MD -20.48 (95% CI -31.55- -9.41)	MD -1.71 (95% CI -3.02 - -0.41)
TCA + Jessner's solution vs. 5-FU **2 studies**	Crude rate	15% (3/20) vs. 35% (7/20) 13.3% (2/15) vs. 46.7% (7/15)	81.7% (201/246) vs. 89.0% (202/227)	79.2±19.5 vs. 89.6±17.4	n.r.
	Effect estimate	RR 0.36 (95% CI 0.14-0.90)	RR 0.92 (95% CI 0.85-0.99)*	MD -10.40 (95% CI -23.63 – 2.83)*	n.r.
GA + 5-FU vs GA **1 study**	Crude rate	22.2% (4/18) vs. 0% (0/18)	92.7% (217/234) vs. 15.8% (39/247)	92.1±5.5 vs. 17.4±8.7	n.r.
	Effect estimate	RR 9.00 (95% CI 0.52-155.86)	RR 5.87 (95% CI 4.39-7.85)	MD 74.70 (95% CI 69.95-79.45)	n.r.
Tretinoin peeling vs. tretinoin cream	-	n.r.	n.r.	n.r.	n.r.

1 study					
Phenol peeling 1 (single arm study)	Crude rate	90.62% (29/32)	n.r.	n.r.	n.r.
5-FU + GA 1 (single arm study)	Crude rate	30% (6/20)	92% (322/350)	n.r.	n.r.

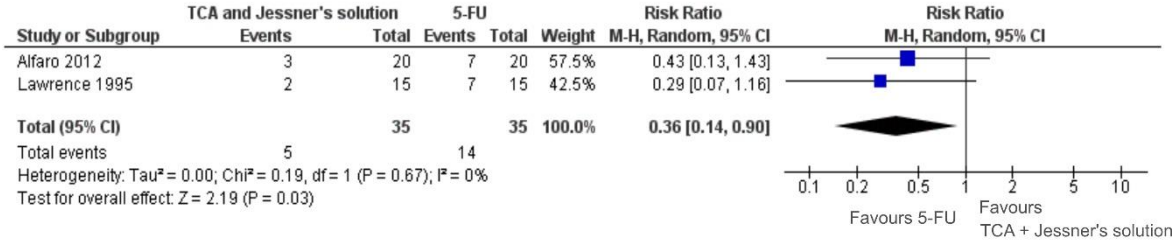
Abbreviations: 5-FU = 5-fluorouracil; CI = confidence interval; GA = glycolic acid; MD = mean difference; PDT = photodynamic therapy; RR = risk ratio; TCA = trichloroacetic acid, VAS = visual analogue scale; vs = versus.

*Only one study reported data for this outcomes.



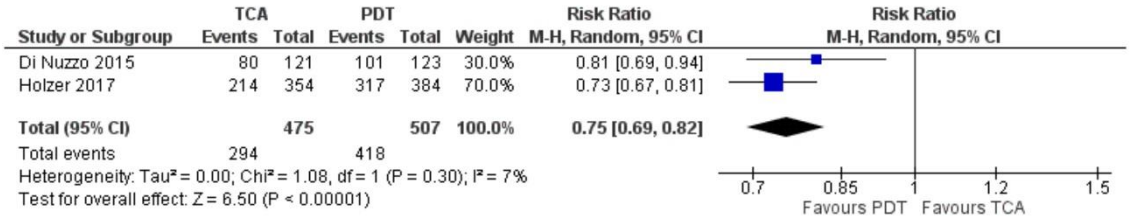
(a) Participant complete clearance

TCA and Jessner's solution vs. 5-FU



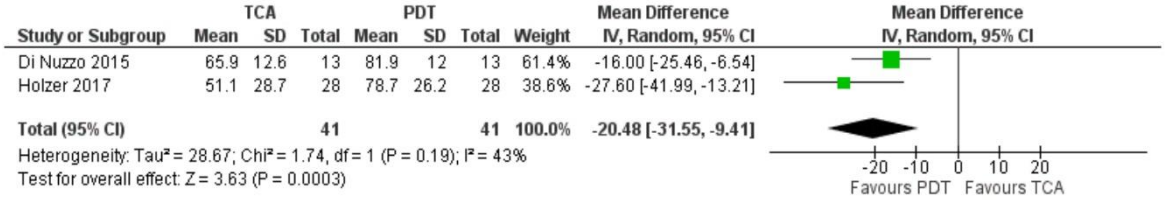
(b) 100% lesion clearance

TCA vs. PDT



(c) Mean lesion clearance per patient

TCA vs. PDT



(d) Pain

TCA vs. PDT