BMJ Open

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019607
Article Type:	Research
Date Submitted by the Author:	13-Sep-2017
Complete List of Authors:	Chen, Xiaomei; Sichuan University West China Hospital, Department of Dermatology & Venereology Wang, Sheng; Sichuan University West China Hospital, Department of Dermatology & Venereology Yang, Ming; The Center of Gerontology and Geriatrics; Li, Li; Sichuan University West China Hospital, Department of Dermatology & Venereology
Keywords:	chemical peeling, acne vulgaris, systematic review, treatment, comedone, papule

Title Page

Title

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Authors

Xiaomei Chen M.D., Sheng Wang M.D., Ming Yang M.D., Li Li M.D.

Affiliations and locations of all authors

Xiaomei Chen: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Sheng Wang: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Ming Yang: The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China

Li Li: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Corresponding author

Li Li, M.D.: Department of Dermatology & Venereology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. Telephone: +86 28 85423315; Fax: +86 28 85423315; Email:

hxskincos2017@qq.com

Word counts

Manuscript: 3895 words

Abstract

Objective: Systematically evaluate current evidence from randomized controlled trials (RCTs) regarding the effectiveness of chemical peeling agents for the treatment acne vulgaris.

Methods: Standard Cochrane methodological procedures were used. We searched MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE via OvidSP through April 2017. Reviewers independently assessed eligibility and risk of bias, and extracted data from the included RCTs. Meta-analysis was not possible due to the significant clinical heterogeneity across studies.

Results: Twelve RCTs (387 participants) were included in our analysis. Effectiveness was equivalent for the following agents: trichloroacetic acid versus salicylic acid (SA); glycolic acid (GA) versus amino fruit acid; SA versus pyruvic acid; GA versus SA; GA versus Jessner's solution (JS); and lipohydroxy acid versus SA. The combination of SA and mandelic acid peels was superior than GA peeling; with GA peeling being superior to a placebo. SA peeling may be superior to JS peeling to treat comedones, but is less effective than phototherapy to treat pustules. The methodological quality of all included RCTs was very low to moderate, with possible biasing of results.

Conclusions: Commonly used chemical peels have similar effectiveness for the treatment of mild-to-moderate acne vulgaris and are well-tolerated. Further evaluation is needed for premixed peels and to identify optimal regimens.

Keywords: chemical peeling; acne vulgaris; systematic review; treatment; comedone; papule; pustule

ARTICLE SUMMARY

- Chemical peeling is widely used for acne vulgaris.
- Chemical peeling is a useful and well-tolerated method for improving acne lesions. Commonly used chemical peels have similar effects, but data regarding premixed peeling agents are limited.
- Premixed peels and optimal regimens need further evaluation.

INTRODUCTION

Acne is one of the most common skin disorders, being prevalent in most ethnic populations around the world.[1] Acne is most prevalent among adolescents, affecting 85% to 90% of adolescents, and may persist into adulthood in some patients.[2 3] Acne vulgaris can negatively affect an individual's appearance and self-esteem, causing anxiety, depression, poor quality of life, and even suicidal ideation. [1 2] The skin lesions of acne vulgaris are classified as either non-inflammatory lesions (comedones) or inflammatory lesions (papules, pustules, nodules, and cysts). The treatment of acne vulgaris includes systemic therapies (oral antibiotics and retinoid), topical therapies (benzoyl peroxide) and physical modalities (laser therapy and chemical peeling).

Chemical peeling is a skin resurfacing procedure commonly used for facial

rejuvenation and esthetics.[3] Chemical peeling, which can be traced back to ancient Egypt, induces a manageable injury to the skin, with subsequent regeneration of a new epidermal layer remodeling of the dermal tissues.[4] The depth of injury is determined by the concentration of acid used, and by the type of vehicle, buffering and contact time with the skin. Chemical peels are, therefore, classified as superficial (destroying the epidermis), moderate (destroying the papillary dermis and upper reticular dermis) or deep (destroying part or all of the mid-reticular dermis).[5] Although often used to treat acne, chemical peeling is also widely used as a cosmetic treatment for melasma, photoaging and lentigines.[5] Superficial peels are generally used for acne vulgaris, whereas deep peels are used to treat acne scars. Commonly used agents for chemical peels are summarized in Table 1.

Table 1. The commonly used chemical peels for acne vulgaris

Chemical peels	Abbreviations
α-hydroxy acid	AHA
Amino fruit acid	AFA
Glycolic acid	GA
Mandelic acid	MA
Tartaric acid	TA
β-hydroxy acid	BHA
Salicylic acid	SA
Azelaic acid	AZA
Lipohydroxy acid	LHA
Jessner's solution*	JS
Pyruvic acid	PA
Retinoic acid	RA
Trichloroacetic acid	TCA

*Jessner's solution is a premixed formula containing 14% salicylic acid, 14% lactic acid, and 14% resorcinol.

The exact pathogenesis of acne vulgaris remains unclear. However, the proliferation of *Propionibacterium* acnes, increased levels of inflammatory cytokines and sebum

production, and follicular hyperkeratinization are all involved.[3] Chemical peels have antibacterial, anti-inflammatory, keratolytic, and comedolytic effects, and can reduce sebum production. Therefore, chemical peels have been widely used in the treatment of acne vulgaris, either as a supplementary or maintenance therapy.[3 5 6]

Despite the wide application of chemical peels in clinical practice, evidence regarding their effectiveness in the treatment of acne vulgaris is limited. In a 2016 recommendation for the treatment of acne vulgaris, chemical peels were supported by level B evidence, namely "inconsistent or limited-quality patient-oriented evidence".[7] This recommendation was based on the evaluation of two trials and previously published guideline, and only included research from the PubMed and the Cochrane Library databases, from May 2006 through September 2014. Therefore, potential evidence from other important medical databases was possibly omitted. In addition, new randomized controlled trials (RCT) have been conducted after September 2014.[8-15] Therefore, we conducted a systematic review to summarize current evidence from the RCTs that regarding the effectiveness of chemical peeling in the treatment of acne vulgaris and to evaluate the validity of the aforementioned recommendations.

METHODS

Systematic search of the literature

This review was performed according to the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA)[16] and the Standard Cochrane methodological procedures.[17] The following databases were

searched up to April 25, 2017, using the strategy summarized in Supplementary Table 1: MEDLINE via OvidSP (from 1946); EMBASE via OvidSP (from 1974); and the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 4.

We also handsearched all bibliographies of included and excluded studies and previous systematic reviews to identify further relevant trials.

Inclusion and exclusion criteria

We included all RCTs addressing any chemical peel (compared to placebo or any other treatment) for the treatment of acne vulgaris in any study population. Excluded were studies that recruited patients with sequelae of acne, such as post-inflammatory dyschromia or scarring, evaluated the combined effects of chemical agents and other therapies, such as laser therapy, were quasi-RCTs, and were not published in English.

Selection of studies

Two authors (X.C. and M.Y.) independently reviewed the titles and abstracts identified from the searches and selected possible relevant studies. After reviewing the full text of these studies, the two authors independently decided on studies to the included and excluded, recording reasons for the exclusion. Any discrepancy in selection was resolved through discussion.

Data extraction

Two authors (X.C. and M.Y.) independently extracted the information from included studies using the "characteristics of included studies form" recommended by the

Cochrane Handbook for Systematic Review of Interventions.[17] Another author (WS) verified and compared the data extraction forms.

Assessment of risk of bias in included trials

Two authors (X.C. and M.Y.) independently evaluated the risk of bias of included trials, using the methods recommended by the Cochrane Handbook for Systematic Review of Interventions.[17] Discrepancies were resolved through discussion. The Cochrane risk of bias for each included trial was classified as low, high, or unclear.

Measure of treatment effects

Dichotomous outcomes (such as the percentage of meaningful improvement of the total number of lesions) were reported, when possible, as risk ratios (RR), with the associated 95% confidence intervals (CI), with continuous outcomes (such as the number of inflammatory lesions) reported as a mean difference (MD), with the associated 95% CI.

Heterogeneity and data synthesis

Because of the significant clinical heterogeneity between the included RCTs, it was not possible to merge the data from different trials for meta-analysis.

RESULTS

Description of studies

We identified 605 articles in the initial search, after removing duplicates. Of these,

586 were discarded after screening the titles and abstracts, leaving 19 studies for full view, with another seven excluded at this stage. Reasons for exclusion were summarized in Supplementary Table 2. Our final analysis included 12 RCTs, providing data from 387 participants. The PRISMA diagram for study selection is presented in Figure 1. Relevant characteristics of the included RCTs are summarized in Table 2.

Table 2. Summary of relevant characteristics of included studies

Studies	Publication year	Study design	Country	Sample size	Women (%)	Fitzpatrick skin type	Severity of acne	Interventions	Main outcomes	Follow-up (weeks)
Abdel et al.[8]	2015	Single-center, double-blind, split-face RCT	Egypt	20	85	III, IV, V	Mild to moderate	25% TCA versus 30% SA	✧ Percentage of total/ good/ fair/ poor improvement of total lesions ✧ Percentage of total/ good/ fair/ poor improvement of non-inflammatory lesions ✧ Percentage of total/ good/ fair/ poor improvement of inflammatory lesions ✧ Reduction of lesion counts ✧ Adverse events	10
Alba et al.[9]	2017	Single-center, single-blind RCT	Brazil	22	41	II, III, IV, VI	Mild to moderate	10% SA versus phototherapy	✧ Comedone counts ✧ Papule counts ✧ Pustule counts	10
Bae et al.[10]	2013	Single-center, single-blind, split-face RCT	Korea	13	0	III or IV	Mild to moderate	30% SA versus JS	✧ Number of non-inflammatory lesions ✧ Number of inflammatory lesions ✧ Self-reported good/ moderate/ mild/ no improvement of all lesions ✧ Adverse events	8
Dayal et al. [11]	2017	Single-center, single-blind RCT	India	40	35	N/A	Mild to moderate	30% SA versus JS	✧ Comedone counts ✧ Overall percentage decrease in mean comedone counts ✧ Papule counts ✧ Overall percentage decrease in mean papule counts ✧ Pustule counts ✧ Overall percentage decrease in mean pustules	12

									counts ✧ Michaelsson acne score (MAS) ✧ Percentage decrease in mean MAS ✧ Percentage of good/ fair/ poor response ✧ Adverse events	
ElRefaei et al. [12]	2015	Single-center, open-label RCT	Egypt	40	80	I, II, III, IV	Mild to very severe	20% SA + 10% MA versus 35% GA	✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of improvement in comedones/ papules/ pustules/ the total acne score ✧ Adverse events	20
Ilknur et al. [18]	2010	Single-center, single-blind, split-face RCT	Turkey	30	N/A	II, III	Mild to moderate	GA versus AFA	✧ Non-inflammatory lesion counts ✧ Inflammatory lesion counts ✧ Patients' choice for the future treatment ✧ Adverse events	24
Jaffary et al. [13]	2016	Multi-center, single-blind RCT	Iran	86	92	N/A	Mild to moderate	30% SA versus 50% PA	✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of excellent/ good/ fair/ poor improvement of all lesions ✧ Acne severity index (ASI) ✧ Percentage of patient satisfaction ✧ Adverse events	8
Kaminaka et al. [14]	2014	Single-center, double-blind, split-face RCT	Japan	25	64	N/A	Moderate to severe	40% GA versus Placebo	✧ Non-inflammatory lesion counts ✧ Inflammatory lesion counts ✧ Total lesion counts ✧ Percentage of excellent/ good/ fair/ bad improvement of all lesions ✧ Bioengineering measurements ✧ Adverse events	10
Kessler et al. [19]	2008	Single-center, double-blind, split-face RCT	American	20	65	N/A	Mild to moderate	30% GA versus 30% SA	✧ Mean number of all lesions ✧ Reduction of all lesions ✧ Percentage of good/ fair/ poor improvement of all lesions	20

Kim et al. [20]	1999	Single-center, single-blind, split-face RCT	Korea	26	84.6	III, IV	Mild to moderate	70% GA versus JS	✧ Self-reported overall improvement ✧ Adverse events ✧ Percentage of patients' who achieving improvement of acne scores of 0.5 or more	8
Leheta et al. [21]	2009	Single-center, single-blind, RCT	Egypt	45	N/A	II, III, IV	Mild to moderate	20% TCA versus PDL	✧ Self-reported overall improvement ✧ Patients' choice for the future treatment ✧ Adverse events ✧ Acne severity score ✧ Mean remission period ✧ Percentage of marked/ moderate response ✧ Self-reported cost-effective ratio ✧ Adverse events	48
Levesque et al. [15]	2011	Single-center, open-label, split-face RCT	American	20	95	N/A	N/A	LHA (5% or 10%) versus SA (20% or 30%)	✧ Reduction of non-inflammatory lesions ✧ Inflammatory lesion counts ✧ Global acne assessment ✧ Adverse events	14

AFA: Amino fruit acid; AZA: Azelaic acid; GA: Glycolic acid; JS: Jessner's solution; LHA: Lipohydroxy acid; MA: Mandelic acid; PA: Pyruvic acid; PDL: pulsed dye laser; RCT: Randomized controlled trial; SA: Salicylic acid: TCA: Trichloroacetic acid.

Risk of bias in included studies

The methodological quality of included RCTs was generally low-to-moderate, and in some cases very low. The risk of bias for each included study is shown in Figure 2, with the percentage of each risk of bias item across studies summarized in Figure 3.

Effects of interventions

Due to significant differences across studies with regard to interventions (different chemical peels and regimens), outcomes and follow-up durations, data from the different studies could not be combined for meta-analysis. In total, we identified eight different chemical peels and grouped the data into 11 comparisons.

Comparison 1: Trichloroacetic acid (TCA) peel versus salicylic acid (SA) peel

One RCT (20 participants, split-face comparison) compared 25% TCA (every two weeks, four sessions) to 30% SA (every two weeks, four sessions) for the treatment of mild-to-moderate acne vulgaris. Skin lesions significantly improved, from baseline, in both treatment groups, with no significant difference between TCA and SA with respect to the percentage of total improvement for all lesions (85% versus 95%; RR 0.89; 95% CI, 0.73-1.10), for non-inflammatory lesions (80% versus 70%; RR 1.14; 95% CI, 0.80-1.64) and for inflammatory lesions (80% versus 85%; RR 0.94; 95% CI, 0.71-1.25).[8]

Adverse events: No adverse event was identified for the SA peel. For the TCA peel, four patients (20%) reported hyperpigmentation, which lasted for 3 to 4 weeks.[8]

Comparison 2: SA peel versus phototherapy

One RCT (22 participants) compared 10% SA (every one week, 10 sessions) to phototherapy (every one week, 10 sessions). Both interventions significantly improved acne lesions, with no significant difference between the two interventions with respect to the reduction in the number of comedones (MD, 2.00; 95% CI, -3.67-7.67) and papules (MD, -1.00; 95% CI, -4.40-2.40). However, the SA peel did not reduce the number of pustules to the same extent as phototherapy (MD, -7.00; 95% CI, -10.84- -3.16).[9]

Adverse events: No information on adverse effects was reported.[9]

Comparison 3: SA peel versus Jessner's solution (JS) peel

Two RCTs compared SA to JS peels.[10 11] Because of significant differences in the treatment regimen, measured outcomes, and follow-up duration, data from these two studies could not be combined for analysis.

One RCT (13 patients, split-face comparison) compared 30% SA (every two weeks, three sessions) to JS (every two weeks, three sessions).[10] The authors stated that SA "seemed to be more effective than" JS for the treatment of non-inflammatory lesions. However, relevant supporting data for this conclusion were not clearly described. As well, the authors reported that both SA and JS were effective for reducing inflammatory lesions; but without comparing the effects of SA and JS on this outcome.

The other RCT (40 patients) also compared 30% SA (every two weeks, six sessions) to JS (every two weeks, six sessions).[11] SA was superior to JS with respect to overall

percentage decrease in the mean number of comedones (53.4% and 26.3%, respectively, p=0.001), with equivalent outcomes for papules (71.0% and 61.5%, respectively, p=0.870) and pustules (70.3% and 76.7%, respectively, p=0.570). The proportional decrease in the mean Michaelsson acne score (MAS), before and after treatment, was greater for SA than JS (60.4% and 34.1%, respectively, p=0.002).

Adverse events: Initial burning sensations, post-peel erythema and mild scaling were common complaints that were comparable for the SA and JS groups.[11] One patient reported intense scaling on the side treated with SA.[10] There was no report of hyperpigmentation.

Dayal et al. reported that SA and JS were both well-tolerated, although SA induced more burning and stinging sensation (65% and 45%, respectively; RR 2.27; 95% CI, 0.64-8.11; non-significant between-group difference).[11] On the other hand, post-peel erythema was less common in the SA group than JS group (20% and 30%, respectively; RR 0.58; 95% CI 0.14-2.50; non-significant between-group difference). Hyperpigmentation was rare in both groups (5% and 15%, respectively; RR 0.30; 95% CI, 0.30-3.15).

Comparison 4: SA plus mandelic acid (MA) peel versus glycolic acid (GA) peel

One RCT (40 patients) compared 20% SA plus 10% MA (every 2 weeks, six sessions) to 35% GA (every 2 weeks, 6 sessions). [12] The combination of SA and MA was superior to GA with respect to the percentage of improvement, from baseline, in comedones (90.2% and 35.9%, respectively, p<0.05), papules (81.7% and77.8%, respectively, p=0.006), and pustules (85.4% and 75.7%, respectively, p<0.001), as

well as for the total acne score (85.3% and 68.5%, respectively, p<0.001).

Adverse events: There was no significant difference between these two intervention groups in terms of burning or stinging sensation (20% and 10%, respectively; RR, 2.00; 95% CI, 0.41-9.71), skin dryness (15% and 10%, respectively; RR, 1.50; 95% CI, 0.28-8.04), and acne flare-up (10% each; RR, 1.00; 95% CI, 0.16-6.42). However, the combination of SA and MA, induced more visible desquamation than GA (80% and 40%, respectively; RR, 2.00; 95% CI, 1.12-3.57).

Comparison 5: GA peel versus amino fruit acid (AFA) peel

One RCT (30 patients, split-face comparison) compared GA (at concentrations of 20%, 35%, 50%, and 70%; every 2 weeks, 12 sessions) to AFA (at similar concentrations of 20%, 30%, 40%, 50%, and 60%; every 2 weeks, 12 sessions). Both peeling agents significantly improved acne lesions, with comparable effectiveness in reducing the number of non-inflammatory lesion counts (MD, 2.35; 95% CI, -18.66-23.36), the reduction of inflammatory lesions (MD, 0.20; 95% CI, -3.03-3.43), and patients' choice of future treatment (GA, 45.8%; AFA, 54.2%; RR, 0.85; 95% CI, 0.48-1.50).

Adverse events: All patients reported erythema at least once for both peels over the follow-up period. Edema was more common for GA than AFA (91.7% and 50%, respectively; RR, 1.83; 95% CI, 1.21-2.78). The incidence of frosting was comparable both GA and AFA peels (29.2% versus 16.7%, respectively; RR, 1.75; 95% CI, 0.59-5.21). Of note, all patients reported a level of discomfort with the GA peel that negatively affected daily life.

Comparison 6: SA peel versus pyruvic acid (PA) peel

One RCT (86 patients) compared 30% SA (every 2 weeks, five sessions) to 50% PA (every 2 weeks, five sessions).[13] The two peels had similar effects for reducing comedones (MD, 7.45; 95% CI, -18.46-33.36), papules (MD, -0.20; 95% CI, -5.36-4.96) and pustules (MD, -1.03; 95% CI, -2.01-0.05). Achievement of an excellent or good improvement of all lesions was comparable for both SA and PA peels (66.7% and 60%, respectively; RR, 1.11; 95% CI, 0.73-1.69).[13]

Adverse events: Burning sensation was very common (>85%) for both peels. The incidence of scaling, erythema or itching was also reported to be comparable for both peels (with no data presented). Hyperpigmentation was rare and comparable for the SA and PA peels (11.1% and 8%, respectively; RR, 1.39; 95% CI, 0.25-7.64).

Comparison 7: GA peel versus placebo

One RCT (25 patients, split-face comparison) compared 40% GA (every 2 weeks, 5 sessions) to a placebo (every 2 weeks, 5 sessions).[14] GA was significantly superior to the placebo for reducing the number of non-inflammatory lesions (no data available, $p<0.01$), inflammatory lesions (no data available, $p<0.01$) and total lesions (no data available, $p<0.01$).[14] Achievement of an excellent or good improvement of all lesions was also superior for GA than the placebo (92% versus 40%, respectively; RR, 2.30; 95% CI, 1.40-3.77).

Adverse events: The authors reported that most patients suffered from "transient post-treatment mild erythema that lasted a few minutes at most", but no supporting data was presented.[14] Mild dryness was less common in the GA than placebo group

(28% and 100%, respectively; RR, 0.29; 95% CI, 0.16-0.54), with the incidence of scaling being comparable between the groups (16% and 12%, respectively; RR, 1.33; 95% CI, 0.33-5.38). A rate of flare-up of 12% was reported of GA, with no flare-up for the placebo, although this difference was not significant (RR, 7.00; 95% CI, 0.38-128.87).

Comparison 8: GA peel versus SA peel

One RCT (20 patients, split-face comparison) compared 30% GA (every 2 weeks, 6 sessions) to 30% SA (every 2 weeks, 6 sessions).[19] Good or fair improvement in the total number of lesions at 1-month post-treatment was achieved with both GA and SA (94.1% each, RR, 1.00; 95% CI, 0.85-1.18). However, the mean number of all lesions was significantly higher on the GA-treated side than on the SA-treated side after a 2-month follow-up of no treatment (no data available, $p<0.01$). In terms of the patients' self-assessment, 41% of patients preferred GA over SA; 35% preferring SA (RR, 1.17; 95% CI, 0.49-2.75).

Adverse events: The authors reported that both GA and SA were safe and well-tolerated, with no difference in the rate of adverse events between the two peels. The most common adverse events were scaling, peeling and erythema (no data available).

Comparison 9: GA peel versus JS peel

One RCT (26 patients, split-face comparison) compared 70% GA (every 2 weeks, 3 sessions) to JS (every 2 weeks, 3 sessions).[20] Both GA and JS had similar effects in

improving acne scores by ≥ 0.5 (50% each; RR, 1.00; 95% CI, 0.58-1.72). Self-reported improvement was equivalent for GA and JS (30.7% and 30.7%, respectively; RR, 1.00; 95% CI, 0.44-2.26), as was the choices for future treatment (50% and 30.7%, respectively; RR, 1.63; 95% CI, 0.81-3.65).

Adverse events: Erythema was common for both peels (no data available). However, JS induced scaling which negatively influenced patients' daily life (GA, 0%; JS, 36%; RR, 0.05; 95% CI, 0-0.86). Two patients failed to tolerate the 70% GA treatment due to the development of acute eczema, crusting and oozing.

Comparison 10: TCA peel versus non-purpuric pulsed dye laser

One RCT (45 patients) compared 25% TCA peel (every 2 weeks, 6 sessions) to non-purpuric pulsed dye laser (every 2 weeks, 6 sessions).[21] The mean acne severity score was significantly improved, from baseline, for both TCA and laser therapy (MD 0.28; 95% CI, -0.33-0.89), with the clinical response being equivalent for both agents (40% and 46.2%, respectively; RR, 0.87; 95% CI, 0.37-2.04). However, the mean remission period after treatment was significantly shorter for TCA than that laser therapy (MD -1.60 months, 95% CI -1.85 - -1.35).

Adverse events: The authors classified adverse events as follows: none; trace; mild; moderate; and severe. No severe adverse events were reported. Two patients (13%) in the TCA peel group and three (23.1%) in the laser therapy group reported moderate adverse events (RR, 0.58; 95% CI, 0.11-2.94). Mild adverse events were reported in six patients (40%) in the TCA peel group and five (38.5%) in the laser therapy group (RR, 1.04; 95% CI, 0.41-2.62). Both treatments were deemed to be well-tolerated.

Comparison 11: Lipohydroxy acid (LHA) peel versus SA peel

One RCT (20 patients) compared LHA (5% or 10%, every 2 weeks, 6 sessions) to SA (20% or 30%, every 2 weeks, 6 sessions).[15] Both LHA and SA reduced the number of non-inflammatory lesions (55.6% and 48.5%, respectively, p=0.878) and inflammatory lesions (no data available, p=0.111).

Adverse events: Both LHA and SA peels were well-tolerated. The global tolerance for the SA peel was better than that for the LHA peel when assessed by patients (no data available, p=0.028), but with no difference when assessed by the investigator (no data available, p=0.546).

DISCUSSION

Based on our analysis of the data presented in the 12 included RCTs, chemical peeling offers an overall positive response for the treatment of acne vulgaris. The following head-to-head comparisons demonstrated the equivalence of the following peels for the treatment of acne vulgaris: TCA versus SA, GA versus AFA, SA versus PA, GA versus SA, GA versus JS, and LHA versus SA. Moreover, the combination of SA and MA provides a more effective peeling than GA. Furthermore, SA was found to be more effective than JS for the treatment of comedones, but less effective than phototherapy to treat pustules. The effectiveness of TCA is comparable to that of pulsed dye laser therapy, but with laser providing a longer period of remission.

All chemical peels evaluated were well-tolerated with the most common adverse events as follows: transient burning or sting sensation; postpeel erythema or scaling;

and topical edema or dryness. A few patients reported an acne flare-up with the combination of SA and MA peel or with GA. Hyperpigmentation was a rare adverse event reported in patients treated with TCA, SA and JS peels. Of note, this CT did not have sufficient power to identify all adverse events, especially for rare adverse events, due to limited sample size.[22]

The information provided in our review may assist dermatologist in selecting most appropriate chemical peels to treat acne vulgaris. However, our findings should be considered with caution as included RCTs were conducted in different countries and recruited individuals of different ethnicities. The choice of chemical peels should be individualized, based on patient's skin type, history of acne or other skin diseases and relevant treatments, and patient's expectations. For example, chemical peels, especially medium or deep peels, are unsuitable for those with a Fitzpatrick skin type V or VI, these peels may cause dyspigmentation and scarring in these patients.[23 24] In fact, most included studies recruited patients with a Fitzpatrick skin type I-IV, although some studies did not report the skin type. In addition, most included studies focused on mild-to-moderate acne.

There is currently no consensus regarding a standardized regimen for chemical peeling, with the optimal concentration, treatment interval, and duration for different chemical peels remaining unclear. Similarly, in our review, the regimen of chemical peels varied significantly across studies. For example, the concentration of GA in different RCTs varied from 10% to 70%, whereas the treatment durations varied from six to 24 weeks. Studies are warranted to compare different regimens of the same

chemical peel in order to determine the optimal regimen for each peeling agent.

There is an emergent trend to using a combination of peeling agents, with the belief that better clinical results can be achieved while reducing the risk of adverse events. [3] As examples, Vitalize Peel contains both SA and lactic acid, with Micropeel Plus containing SA and GA. include acne vulgaris. [5] However, we failed to find any RCT to confirm the efficacy of the premixed chemical peeling agents for acne. In the future, more attention should be paid to these premixed formulating of chemical peels.

The limitations of our review need acknowledgement. First, all included studies were of very low-to-moderate methodological quality, with small sample sizes, which might induce bias, which we evaluated for each study. As an example, most of the included RCTs did not describe the method of randomization. Adherence to the recommendations from the Consolidated Standards of Reporting Trials (CONSORT) Statement would be important to avoid incomplete and inadequate reporting and improve the quality of the evidence.[25] Second, this review did not cover the effects of chemical peeling for acne scarring, although chemical peels are used clinically for this indication.[26] Lastly, as previously discussed, absence of standardization of peeling regiment limits the translation of our findings to practice.

In conclusion, current evidence supports chemical peeling as a useful and well-tolerated intervention for the treatment of mild-to-moderate acne vulgaris. Commonly used chemical peels have similar effects. However, there is limited data regarding premixed chemical peels for acne vulgaris. Well-designed and well-reported RCTs are needed to provide high quality evidence to inform practice, particularly in

regard to optimal formulation and regiment of chemical peeling agents for various ethnic populations and skin types.

ACKNOWLEDGEMENT

None.

COMPETING INTERESTS

All authors have not conflict of interest to declare.

CONTRIBUTORS

XC and LL designed the protocol. XC and MY searched the literature, extracted the data, and analysed the data. XC, SW, MY and LL interpreted the data and revised the manuscript.

FUNDING

This review was supported by a grant from the Sichuan Provincial Science and Technology Department (Grant number: 2017JY0277).

DISCLAIMER

The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report.

REFERENCES

1. Sathish D, Shayeda, Rao YM. Acne and its treatment options: a review. *Curr*

Drug Deliv 2011;8(6):634-9.

2. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013;168(3):474-85. doi: 10.1111/bjd.12149

3. Kontochristopoulos G, Platsidaki E. Chemical peels in active acne and acne scars. *Clinics in Dermatology* 2017;35(2):179-82.

4. Salam A, Dadzie OE, Galadari H. Chemical peeling in ethnic skin: an update. *British Journal of Dermatology* 2013;169 Suppl 3:82-90.

5. Jackson A. Chemical peels. *Facial Plast Surg* 2014;30(1):26-34. doi: 10.1055/s-0033-1364220

6. Dreno B, Fischer TC, Perosino E, et al. Expert opinion: efficacy of superficial chemical peels in active acne management--what can we learn from the literature today? Evidence-based recommendations. *Journal of the European Academy of Dermatology & Venereology* 2011;25(6):695-704.

7. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74(5):945-73 e33. doi: 10.1016/j.jaad.2015.12.037

8. Abdel Meguid AM, Elaziz Ahmed Attallah DA, Omar H. Trichloroacetic Acid Versus Salicylic Acid in the Treatment of Acne Vulgaris in Dark-Skinned Patients. *Dermatologic Surgery* 2015;41(12):1398-404.

9. Alba MN, Gerenutti M, Yoshida VM, et al. Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne

vulgaris in teenagers. *Journal of Cosmetic & Laser Therapy* 2017;19(1):49-53.

10. Bae BG, Park CO, Shin H, et al. Salicylic acid peels versus Jessner's solution for acne vulgaris: a comparative study. *Dermatologic Surgery* 2013;39(2):248-53.
11. Dayal S, Amrani A, Sahu P, et al. Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. *J Cosmet Dermatol* 2017;16(1):43-51. doi: 10.1111/jocd.12266
12. ElRefaei AM, Abdel Salam HA, Sorour NE. Salicylic-mandelic acid versus glycolic acid peels in Egyptian patients with acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society* 2015;12(3):196-202.
13. Jaffary F FGSSHSM. Comparison the effectiveness of pyruvic acid 50% and salicylic acid 30% in the treatment of acne. *Journal of research in medical sciences* 2016;21(2)
14. Kaminaka C, Uede M, Matsunaka H, et al. Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. *Dermatologic Surgery* 2014;40(3):314-22.
15. Levesque A, Hamzavi I, Seite S, et al. Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. *Journal*

of Cosmetic Dermatology 2011;10(3):174-8.

16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535. doi: 10.1136/bmj.b2535

17. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011 [Available from: www.handbook.cochrane.org.

18. Ilknur T, Demirtasoglu M, Bicak MU, et al. Glycolic acid peels versus amino fruit acid peels for acne. *Journal of Cosmetic & Laser Therapy* 2010;12(5):242-5.

19. Kessler E, Flanagan K, Chia C, et al. Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. *Dermatologic Surgery* 2008;34(1):45-50; discussion 51.

20. Kim SW, Moon SE, Kim JA, et al. Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. *Dermatologic Surgery* 1999;25(4):270-3.

21. Leheta TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. *Journal of Cosmetic & Laser Therapy* 2009;11(2):118-24.

22. Wahab IA, Pratt NL, Kalisch LM, et al. The detection of adverse events in

randomized clinical trials: can we really say new medicines are safe? *Current drug safety* 2013;8(2):104-13. [published Online First: 2013/05/30]

23. Been MJ, Mangat DS. Laser and face peel procedures in non-Caucasians. *Facial Plastic Surgery Clinics of North America* 2014;22(3):447-52.

24. Handog EB, Datuin MS, Singzon IA. Chemical peels for acne and acne scars in asians: evidence based review. *Journal of Cutaneous & Aestheic Surgery* 2012;5(4):239-46.

25. Boutron I, Altman DG, Moher D, et al. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med* 2017;167(1):40-47. doi: 10.7326/M17-0046

26. Abdel Hay R, Shalaby K, Zaher H, et al. Interventions for acne scars. *Cochrane Database of Systematic Reviews* 2016(pagination)

FIGURE LEGEND

Figure 1. The Preferred Reporting Items for Systematic Reviews (PRISMA) diagram of the study flow.

Figure 2. Risk of bias summary for each study.

Figure 3. Risk of bias summary graph of all included studies.

SUPPLEMENTARY FILES

Supplementary Table 1. The search strategies for MEDLINE, EMBASE and CENTRAL via OvidSP.

Supplementary Table 2. Reasons for the exclusion of studies

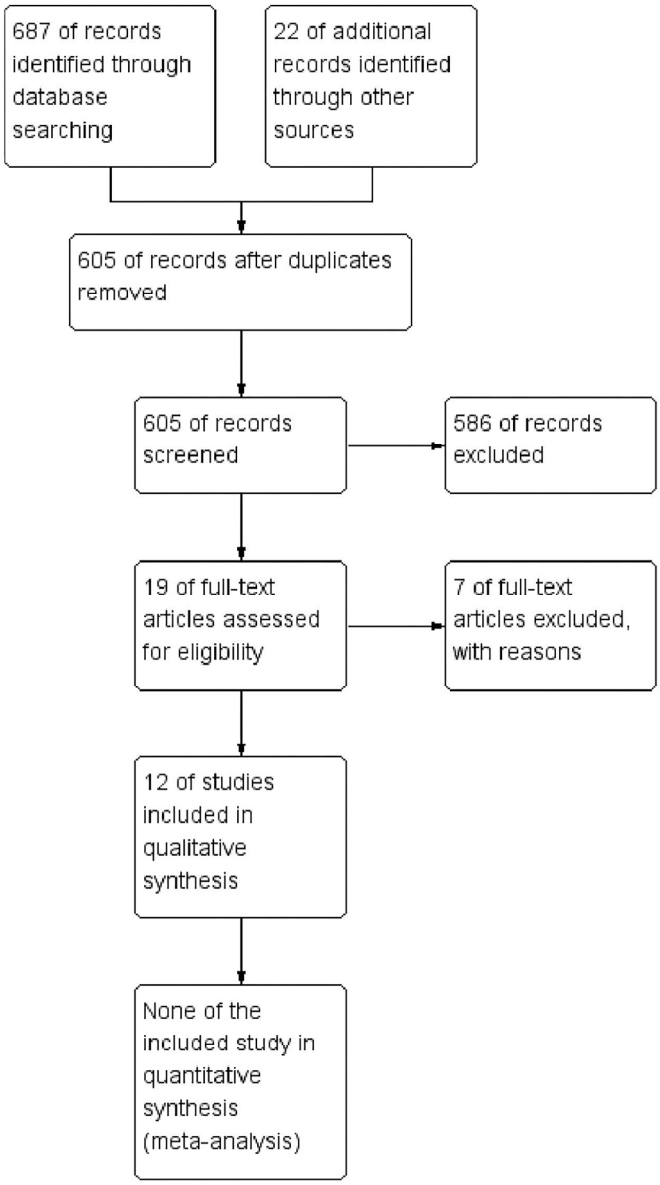

Figure 1. The Preferred Reporting Items for Systematic Reviews (PRISMA) diagram of the study flow.

176x297mm (300 x 300 DPI)

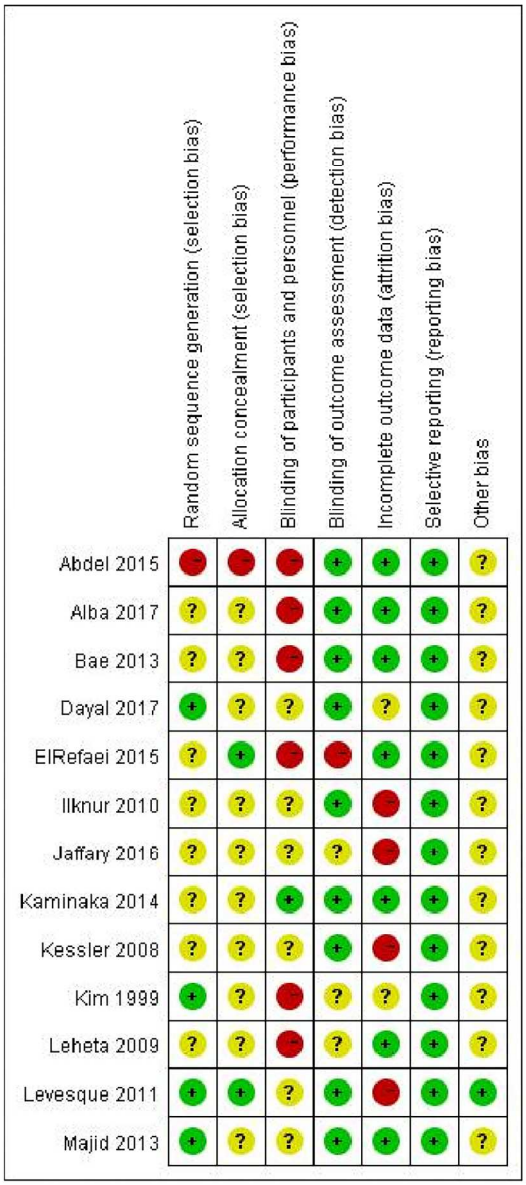

Figure 2. Risk of bias summary for each study.

138x297mm (300 x 300 DPI)

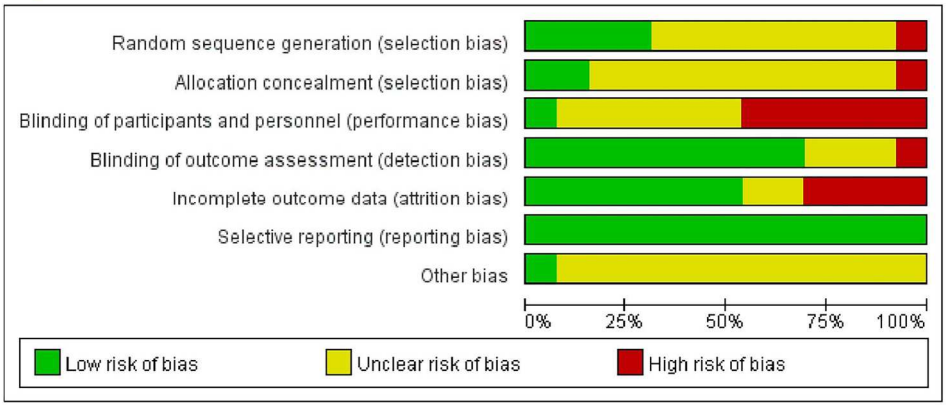

Figure 3. Risk of bias summary graph of all included studies.

209x87mm (300 x 300 DPI)

Supplementary Table 1. The search strategies for searching MEDLINE, EMBASE, and CENTRAL via OvidSP

No.	Searches
1	(chemical adj (peel* or resurface*).ab,kw,ti.
2	((hydroxy or glycolic or lactic or malic or citric or tartaric or salicylic or trichloroacetic or pyruvic or lipohydroxy or salicylic-mandelic or "amino fruit") adj acid*).ab,kw,ti.
3	("Jessner's solution" or "Jessner's solutions").ab,kw,ti.
4	(resorcinol* or phenol*).ab,kw,ti.
5	acne.ab,kw,ti.
6	exp *Acne Vulgaris/
7	1 or 2 or 3 or 4
8	5 or 6
9	7 and 8
10	remove duplicates from 9

Supplementary Table 2. Characteristics of excluded studies

Studies	Reason for exclusion
Garg 2009 [1]	This study is not an RCT.
Kim 2015 [2]	This RCT compared alpha hydroxy acids plus an additional physical treatment with alpha hydroxy acids alone.
Lee 2006 [3]	This study is not an RCT.
Lekakh 2015 [4]	This study compared chemical peel and the combination of laser and chemical peel.
Nofal 2014 [5]	This study appears to be not an RCT because of the significant difference between the method section and the abstract about the randomization. And there is no reply from the authors to clarify this inconsistency.
Sharad 2011 [6]	This study is not an RCT
Wang 1997 [7]	This study is not an RCT

RCT: randomized controlled trial.

References of the excluded studies:

1. Garg VK, Sinha S , Sarkar R. Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: a comparative study. Dermatologic Surgery 2009;35:59-65.

2. Kim SJ, Baek JH, Koh JS, Bae MI, Lee SJ , Shin MK. The effect of physically applied

alpha hydroxyl acids on the skin pore and comedone. International Journal of Cosmetic Science 2015;37:519-25.

3. Lee SH, Huh CH, Park KC , Youn SW. Effects of repetitive superficial chemical peels on facial sebum secretion in acne patients. Journal of the European Academy of Dermatology & Venereology 2006;20:964-8.

4. Lekakh O, Mahoney AM, Novice K, Kamalpour J, Sadeghian A, Mondo D et al. Treatment of Acne Vulgaris With Salicylic Acid Chemical Peel and Pulsed Dye Laser: A Split Face, Rater-Blinded, Randomized Controlled Trial. Journal of Lasers in Medical Sciences 2015;6:167-70.

5. Nofal E, Helmy A, Nofal A, Alakad R , Nasr M. Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: a comparative study. Dermatologic Surgery 2014;40:864-73.

6. Sharad J. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. Journal of Cosmetic Dermatology 2011;10:317-23.

7. Wang CM, Huang CL, Hu CT , Chan HL. The effect of glycolic acid on the treatment of acne in Asian skin. Dermatologic Surgery 1997;23:23-9.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not necessary

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not necessary
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Meta-analysis is not possible to be performed.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not necessary
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019607.R1
Article Type:	Research
Date Submitted by the Author:	14-Feb-2018
Complete List of Authors:	Chen, Xiaomei; Sichuan University West China Hospital, Department of Dermatology & Venereology Wang, Sheng; Sichuan University West China Hospital, Department of Dermatology & Venereology Yang, Ming; The Center of Gerontology and Geriatrics; Li, Li; Sichuan University West China Hospital, Department of Dermatology & Venereology
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Evidence based practice, Infectious diseases
Keywords:	chemical peeling, acne vulgaris, systematic review, treatment, comedone, papule

Title Page

Title

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Authors

Xiaomei Chen M.D., Sheng Wang M.D., Ming Yang M.D., Li Li M.D.

Affiliations and locations of all authors

Xiaomei Chen: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Sheng Wang: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Ming Yang: The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China

Li Li: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Corresponding author

Li Li, M.D.: Department of Dermatology & Venereology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. Telephone: +86 28 85423315; Fax: +86 28 85423315; Email:

hxskincos2017@qq.com

Word counts

Manuscript: 4338 words

Abstract

Objective: We evaluated current evidence from randomized controlled trials (RCTs) regarding the effectiveness of chemical peeling for treating acne vulgaris.

Methods: Standard Cochrane methodological procedures were used. We searched MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE via OvidSP through April 2017. Reviewers independently assessed eligibility and risk of bias, and extracted data.

Results: Twelve RCTs (387 participants) were included. Effectiveness was equivalent for trichloroacetic acid versus salicylic acid (SA), glycolic acid (GA) versus amino fruit acid, SA versus pyruvic acid, GA versus SA, GA versus Jessner's solution (JS), and lipohydroxy acid versus SA. Combination of SA and mandelic acid peels was superior to GA peeling. GA peeling was superior to placebo. SA peeling may be superior to JS peeling for comedones, but it is less effective than phototherapy fot pustules. The methodological quality of all RCTs was very low to moderate.

Conclusions: Commonly used chemical peels have similar effectiveness for mild to moderate acne vulgaris and are well tolerated. Further evaluation is needed to identify optimal regimens.

Keywords: chemical peeling; acne vulgaris; systematic review; treatment; comedone; papule; pustule

Strengths and limitations of this study

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA) protocols and Cochrane methodological procedures. We could not perform a meta-analysis due to the significant heterogeneity across the RCTs.

ARTICLE SUMMARY

- Chemical peeling is widely used for acne vulgaris.
- Chemical peeling is a useful and well-tolerated method for improving acne lesions. Commonly used chemical peels have similar effects, but data regarding premixed peeling agents are limited.
- Premixed peels and optimal regimens need further evaluation.

INTRODUCTION

Acne is one of the most common skin disorders and is prevalent in most ethnic populations.[1] Acne affects 85% to 90% of adolescents, and may persist into adulthood.[2 3] Acne vulgaris can negatively affect an individual's appearance and self-esteem, thereby causing anxiety, depression, poor quality of life, and even suicidal thought. [1 2] Skin lesions of acne vulgaris are classified as either non-inflammatory (comedones) or inflammatory (papules, pustules, nodules, and cysts). Acne vulgaris treatments include systemic therapies (oral antibiotics and

retinoid), topical therapies (benzoyl peroxide) and physical modalities (laser therapy and chemical peeling).

Chemical peeling is a skin resurfacing procedure commonly used for facial rejuvenation and esthetics.[3] It causes a manageable injury to the skin, thus resulting in sbsequent regeneration of a new epidermal layer of the dermal tissues.[4] The injury depth is determined by the concentration of acid used, and by the type of vehicle, buffering and contact time with the skin. Therefore, chemical peels are, therefore, classified as superficial (destroying the epidermis), moderate (destroying the papillary dermis and upper reticular dermis) or deep (destroying part or all of the mid-reticular dermis).[5] Although often used to treat acne, chemical peeling is also widely used as a cosmetic treatment for melasma, photoaging and lentigines.[5] Superficial peels are generally used for acne vulgaris, whereas deep peels are used to treat acne scars. Commonly used agents for chemical peels are summarized in Table 1.

Table 1. Commonly used chemical peels for acne vulgaris

Chemical peels	Abbreviations
α-Hydroxy acid	AHA
Amino fruit acid	AFA
Glycolic acid	GA
Mandelic acid	MA
Tartaric acid	TA
β-Hydroxy acid	BHA
Salicylic acid	SA
Azelaic acid	AZA
Lipohydroxy acid	LHA
Jessner's solution*	JS
Pyruvic acid	PA
Retinoic acid	RA
Trichloroacetic acid	TCA

*Jessner's solution is a premixed formula containing 14% salicylic acid, 14% lactic acid, and 14% resorcinol.

The exact pathogenesis of acne vulgaris remains unclear. However, the proliferation of *Propionibacterium* acnes, increased levels of inflammatory cytokines and sebum production, and follicular hyperkeratinization are involved.[3] Chemical peels have antibacterial, anti-inflammatory, keratolytic, and comedolytic effects, and they can reduce sebum production. Therefore, chemical peels have been widely used to treat acne vulgaris, either as a supplementary therapy or as a maintenance therapy.[3 5 6]

Despite their wide application, evidence regarding the effectiveness of chemical peels to treat acne vulgaris is limited. A 2016 recommendation for the treatment of acne vulgaris indicated that chemical peels were supported by level B evidence, namely "inconsistent or limited-quality patient-oriented evidence".[7] This recommendation was based on the evaluation of two trials [8 9] and a previously published guideline [6], and it only included research from the PubMed and the Cochrane Library databases, from May 2006 to September 2014. Therefore, potential evidence from other important medical databases was possibly omitted. In addition, new randomized controlled trials (RCTs) were performed after September 2014.[9-16] Therefore, we performed a systematic review to summarize current evidence regarding the effectiveness of chemical peeling for acne vulgaris and to evaluate the validity of the aforementioned recommendations.

METHODS

Systematic search of the literature

This review was performed according to the guidelines for the Preferred Reporting

Items for Systematic Reviews and Meta-Analysis protocols (PRISMA)[17] and the Standard Cochrane methodological procedures.[18] The following databases were searched up to April 25, 2017, using the strategy summarized in Supplementary Table 1: MEDLINE via OvidSP (from 1946); EMBASE via OvidSP (from 1974); and the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 4.

We also hand-searched all bibliographies of the included and excluded studies and previous systematic reviews to identify further relevant trials.

Inclusion and exclusion criteria

We included all RCTs addressing any chemical peel (compared to placebo or any other treatment) for the treatment of acne vulgaris in any study population. Studies that recruited patients with sequelae of acne, such as post-inflammatory dyschromia or scarring, evaluated the combined effects of chemical agents and other therapies, such as laser therapy, were quasi-RCTs, and were not published in English were excluded.

Selection of studies

Two authors (X.C. and M.Y.) independently reviewed the titles and abstracts identified from the searches and selected possible relevant studies. After reviewing the full text of these studies, the two authors independently decided on which studies to included and excluded and record reasons for exclusion. Any discrepancy in selection was resolved through discussion.

Data extraction

Two authors (X.C. and M.Y.) independently extracted the information from the included studies using the "characteristics of included studies form" recommended by the Cochrane Handbook for Systematic Review of Interventions.[18] Another author (WS) verified and compared the data extraction forms.

Assessment of the risk of bias in included trials

Two authors (X.C. and M.Y.) independently evaluated the risk of bias of the included trials by using the methods recommended by the Cochrane Handbook for Systematic Review of Interventions.[18] Discrepancies were resolved through discussion. The Cochrane risk of bias for each included trial was classified as low, high, or unclear.

Measure of treatment effects

Dichotomous outcomes (such as the percentage of meaningful improvement in the total number of lesions) were reported, when possible, as risk ratios (RRs), with the associated 95% confidence intervals (CIs). Continuous outcomes (such as the number of inflammatory lesions) were reported as the mean difference (MD), with the associated 95% CI.

Heterogeneity and data synthesis

Significant clinical heterogeneity across the included RCTs was identified. Specifically, the skin type of participants, interventions (e.g., the type, concentration,

and regimen of chemical peeling agents), and outcome measurements were all significantly different across the included RCTs. Therefore, it was not possible to merge data from different trials to perform a meta-analysis.

RESULTS

Description of studies

After removing duplicates, we identified 605 articles during the initial search. Of these, 586 were discarded after screening the titles and abstracts, leaving 19 studies for full review. Another seven were excluded after this review. Reasons for exclusion are summarized in Supplementary Table 2. Our final analysis included 12 RCTs, providing data from 387 participants. The PRISMA diagram for study selection is presented in Figure 1. Relevant characteristics of the included RCTs are summarized in Table 2.

Table 2. Summary of relevant characteristics of included studies

Studies	Publication year	Study design	Country	Sample size	Women (%)	Fitzpatrick skin type	Acne severity	Interventions	Main outcomes	Follow-up (weeks)
Abdel et al.[10]	2015	Single-center, double-blind, split-face RCT	Egypt	20	85	III, IV, V	Mild to moderate	25% TCA versus 30% SA	✧ Percentage of total/ good/ fair/ poor improvement in total lesions ✧ Percentage of total/ good/ fair/ poor improvement in non-inflammatory lesions ✧ Percentage of total/ good/ fair/ poor improvement in inflammatory lesions ✧ Reduction of lesion counts ✧ Adverse events	10
Alba et al.[11]	2017	Single-center, single-blind RCT	Brazil	22	41	II, III, IV, VI	Mild to moderate	10% SA versus phototherapy	✧ Comedone counts ✧ Papule counts ✧ Pustule counts	10
Bae et al.[12]	2013	Single-center, single-blind, split-face RCT	Korea	13	0	III or IV	Mild to moderate	30% SA versus JS	✧ Number of non-inflammatory lesions ✧ Number of inflammatory lesions ✧ Self-reported good/ moderate/ mild/ no improvement in all lesions ✧ Adverse events	8
Dayal et al. [13]	2017	Single-center, single-blind RCT	India	40	35	N/A	Mild to moderate	30% SA versus JS	✧ Comedone counts ✧ Overall percentage decrease in mean comedone counts ✧ Papule counts ✧ Overall percentage decrease in mean papule counts ✧ Pustule counts ✧ Overall percentage decrease in mean pustules	12

									counts ✧ MAS ✧ Percentage decrease in mean MAS ✧ Percentage of good/ fair/ poor response ✧ Adverse events	
ElRefaei et al. [14]	2015	Single-center, open-label RCT	Egypt	40	80	I, II, III, IV	Mild to very severe	20% SA + 10% MA versus 35% GA	✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of improvement in comedones/ papules/ pustules/ the total acne score ✧ Adverse events	20
Ilknur et al. [8]	2010	Single-center, single-blind, split-face RCT	Turkey	30	N/A	II, III	Mild to moderate	GA versus AFA	✧ Non-inflammatory lesion counts ✧ Inflammatory lesion counts ✧ Patients' choice for the future treatment ✧ Adverse events	24
Jaffary et al. [15]	2016	Multi-center, single-blind RCT	Iran	86	92	N/A	Mild to moderate	30% SA versus 50% PA	✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of excellent/ good/ fair/ poor improvement of all lesions ✧ Acne severity index (ASI) ✧ Percentage of patient satisfaction ✧ Adverse events	8
Kaminaka et al. [16]	2014	Single-center, double-blind, split-face RCT	Japan	25	64	N/A	Moderate to severe	40% GA versus Placebo	✧ Non-inflammatory lesion counts ✧ Inflammatory lesion counts ✧ Total lesion counts ✧ Percentage of excellent/ good/ fair/ bad improvement in all lesions ✧ Bioengineering measurements ✧ Adverse events	10
Kessler et al. [19]	2008	Single-center, double-blind, split-face RCT	United States	20	65	N/A	Mild to moderate	30% GA versus 30% SA	✧ Mean number of all lesions ✧ Reduction of all lesions ✧ Percentage of good/ fair/ poor improvement in all lesions	20

Kim et al. [20]	1999	Single-center, single-blind, split-face RCT	Korea	26	84.6	III, IV	Mild to moderate	70% GA versus JS	✧ Self-reported overall improvement ✧ Adverse events ✧ Percentage of patients' who achieved improvement in acne scores of 0.5 or more	8
Leheta et al. [21]	2009	Single-center, single-blind, RCT	Egypt	45	N/A	II, III, IV	Mild to moderate	20% TCA versus PDL	✧ Self-reported overall improvement ✧ Patients' choice for the future treatment ✧ Adverse events ✧ Acne severity score ✧ Mean remission period ✧ Percentage of marked/ moderate response ✧ Self-reported cost-effectiveness ratio	48
Levesque et al. [9]	2011	Single-center, open-label, split-face RCT	United States	20	95	N/A	N/A	LHA (5% or 10%) versus SA (20% or 30%)	✧ Adverse events ✧ Reduction of non-inflammatory lesions ✧ Inflammatory lesion counts ✧ Global acne assessment ✧ Adverse events	14

AFA: Amino fruit acid; AZA: Azelaic acid; GA: Glycolic acid; JS: Jessner's solution; LHA: Lipohydroxy acid; MA: Mandelic acid; N/A: not available; PA: Pyruvic acid; PDL: pulsed dye laser; RCT: Randomized controlled trial; SA: Salicylic acid: TCA: Trichloroacetic acid.

Risk of bias in included studies

The methodological quality of included RCTs was generally low to moderate; however, in some cases, it was very low. The risk of bias in each included study is shown in Figure 2, with the percentage of each risk of bias item across studies summarized in Figure 3.

Effects of interventions

Due to significant differences across studies with regard to interventions (different chemical peels and regimens), outcomes and follow-up durations, data from the different studies could not be combined to perform a meta-analysis. We identified a total of eight different chemical peels and grouped the data into 11 comparisons.

Comparison 1: Trichloroacetic acid peel versus salicylic acid peel

One RCT (20 participants, split-face comparison) compared 25% trichloroacetic acid TCA (every 2 weeks, 4 sessions) to 30% salicylic acid (SA; every 2 weeks, 4 sessions) for the treatment of mild-to-moderate acne vulgaris. Skin lesions significantly improved, from baseline, in both treatment groups, with no significant difference between TCA and SA regarding the percentage of total improvement for all lesions (85% versus 95%; RR 0.89; 95% CI, 0.73-1.10), for non-inflammatory lesions (80% versus 70%; RR 1.14; 95% CI, 0.80-1.64) and for inflammatory lesions (80% versus 85%; RR 0.94; 95% CI, 0.71-1.25).[10]

Adverse events

No adverse event was identified for the SA peel. For the TCA peel, four patients (20%) reported hyperpigmentation that lasted for 3 to 4 weeks.[10]

Comparison 2: SA peel versus phototherapy

One RCT (22 participants) compared 10% SA (once every week, 10 sessions) to phototherapy (once every week, 10 sessions). Both interventions significantly improved acne lesions, with no significant difference between the two interventions regarding the reduction in the number of comedones (MD, 2.00; 95% CI, -3.67 to7.67) and papules (MD, -1.00; 95% CI, -4.40 to 2.40). However, the SA peel did not reduce the number of pustules to the same extent as phototherapy (MD, -7.00; 95% CI, -10.84 to -3.16).[11]

Adverse events

No information regarding adverse effects was reported.[11]

Comparison 3: SA peel versus Jessner's solution peel

Two RCTs compared SA to Jessner's solution (JS) peels.[12 13] Because of significant differences in the treatment regimen, measured outcomes, and follow-up duration, data from these two studies could not be combined for analysis.

One RCT (13 patients, split-face comparison) compared 30% SA (every 2 weeks, 3 sessions) to JS (every 2 weeks, 3 sessions).[12] The authors stated that SA "seemed to be more effective than" JS for the treatment of non-inflammatory lesions. However, relevant data supporting this conclusion were not clearly described. Furthermore, the authors reported that both SA and JS were effective for reducing inflammatory lesions;

however, they did not compare the effects of SA and JS on this outcome.

Another RCT (40 patients) also compared 30% SA (every 2 weeks, 6 sessions) to JS (every 2 weeks, 6 sessions).[13] SA was superior to JS regarding overall percentage decrease in the mean number of comedones (53.4% and 26.3%, respectively, p=0.001), with equivalent outcomes for papules (71.0% and 61.5%, respectively, p=0.870) and pustules (70.3% and 76.7%, respectively, p=0.570). The proportional decreases in the mean Michaelsson acne score (MAS), before and after treatment, were greater for SA than for JS (60.4% and 34.1%, respectively, p=0.002).

Adverse events

Initial burning sensations, post-peel erythema and mild scaling were common symptoms that were comparable for the SA and JS groups.[13] One patient reported intense scaling on the side that was treated with SA.[12] There was no report of hyperpigmentation.

Dayal et al. reported that SA and JS were both well-tolerated, although SA induced more burning and stinging sensation (65% and 45%, respectively; RR 2.27; 95% CI, 0.64-8.11; non-significant between-group difference).[13] However, post-peel erythema was less common in the SA group than in the JS group (20% and 30%, respectively; RR 0.58; 95% CI 0.14-2.50; non-significant between-group difference). Hyperpigmentation was rare in both groups (5% and 15%, respectively; RR 0.30; 95% CI, 0.30-3.15).

Comparison 4: SA plus mandelic acid peel versus glycolic acid peel

One RCT (40 patients) compared 20% SA plus 10% mandelic acid (MA; every 2

weeks, 6 sessions) to 35% glycolic acid (GA; every 2 weeks, 6 sessions). [14] The combination of SA and MA was superior to GA regarding the percentage of improvement, from baseline, in comedones (90.2% and 35.9%, respectively, p<0.05), papules (81.7% and77.8%, respectively, p=0.006), and pustules (85.4% and 75.7%, respectively, p<0.001), as well as in the total acne score (85.3% and 68.5%, respectively, p<0.001).

Adverse events

There was no significant difference between these two intervention groups in terms of burning or stinging sensations (20% and 10%, respectively; RR, 2.00; 95% CI, 0.41-9.71), skin dryness (15% and 10%, respectively; RR, 1.50; 95% CI, 0.28-8.04), and acne flare-up (10% each; RR, 1.00; 95% CI, 0.16-6.42). However, the combination of SA and MA, induced more visible desquamation than GA (80% and 40%, respectively; RR, 2.00; 95% CI, 1.12-3.57).

Comparison 5: GA peel versus amino fruit acid peel

One RCT (30 patients, split-face comparison) compared GA (at concentrations of 20%, 35%, 50%, and 70%; every 2 weeks, 12 sessions) to amino fruit acid (AFA) (at similar concentrations of 20%, 30%, 40%, 50%, and 60%; every 2 weeks, 12 sessions). [8] Both peeling agents significantly improved acne lesions and had comparable effectiveness in reducing the number of non-inflammatory lesion counts (MD, 2.35; 95% CI, -18.66 to 23.36), the reduction of inflammatory lesions (MD, 0.20; 95% CI, -3.03 to 3.43), and patient's choice of future treatment (GA, 45.8%; AFA, 54.2%; RR, 0.85; 95% CI, 0.48-1.50).

Adverse events: All patients reported erythema at least once for both peels during the follow-up period. Edema was more common for GA than for AFA (91.7% and 50%, respectively; RR, 1.83; 95% CI, 1.21-2.78).[8] The incidence of frosting was comparable for both GA and AFA peels (29.2% versus 16.7%, respectively; RR, 1.75; 95% CI, 0.59-5.21). Of note, all patients reported discomfort that negatively affected daily life with the GA peel.

Comparison 6: SA peel versus pyruvic acid peel

One RCT (86 patients) compared 30% SA (every 2 weeks, five sessions) to 50% pyruvic acid (PA; every 2 weeks, 5 sessions).[15] The two peels had similar effects for reducing comedones (MD, 7.45; 95% CI, -18.46 to 33.36), papules (MD, -0.20; 95% CI, -5.36 to 4.96) and pustules (MD, -1.03; 95% CI, -2.01 to 0.05). Achievement of an excellent or good improvement in all lesions was comparable for both SA and PA peels (66.7% and 60%, respectively; RR, 1.11; 95% CI, 0.73-1.69).[15]

Adverse events

Burning sensations were very common (>85%) for both peels. The incidences of scaling, erythema and itching were also reported to be comparable for both peels (with no data presented). Hyperpigmentation was rare and comparable for the SA and PA peels (11.1% and 8%, respectively; RR, 1.39; 95% CI, 0.25-7.64).

Comparison 7: GA peel versus placebo

One RCT (25 patients, split-face comparison) compared 40% GA (every 2 weeks, 5 sessions) to a placebo (every 2 weeks, 5 sessions).[16] GA was significantly superior to

the placebo for reducing the number of non-inflammatory lesions (no data available, p<0.01), inflammatory lesions (no data available, p<0.01) and total lesions (no data available, p<0.01).[16] Achievement of excellent or good improvement in all lesions was also superior for GA than for placebo (92% versus 40%, respectively; RR, 2.30; 95% CI, 1.40-3.77).

Adverse events

The authors reported that most patients experienced "transient post-treatment mild erythema that lasted a few minutes at most", but no supporting data were presented.[16] Mild dryness was less common in the GA group than in the placebo group (28% and 100%, respectively; RR, 0.29; 95% CI, 0.16-0.54); however, with the incidence of scaling was comparable between the groups (16% and 12%, respectively; RR, 1.33; 95% CI, 0.33-5.38). A flare-up rate of 12% was reported for GA, with no flare-up reported for the placebo, although this difference was not significant (RR, 7.00; 95% CI, 0.38-128.87).

Comparison 8: GA peel versus SA peel

One RCT (20 patients, split-face comparison) compared 30% GA (every 2 weeks, 6 sessions) to 30% SA (every 2 weeks, 6 sessions).[19] Good or fair improvement in the total number of lesions at 1-month post-treatment was achieved with both GA and SA (94.1% each, RR, 1.00; 95% CI, 0.85-1.18). However, the mean number of all lesions was significantly higher on the GA-treated side than on the SA-treated side after a 2-month follow-up with no treatment (no data available, p<0.01). In terms of the patients' self-assessments, 41% of patients preferred GA over SA and 35% preferred

SA (RR, 1.17; 95% CI, 0.49-2.75).

Adverse events

The authors reported that both GA and SA were safe and well-tolerated, with no difference in adverse events rates between the two peels. The most common adverse events were scaling, peeling and erythema (no data available).

Comparison 9: GA peel versus JS peel

One RCT (26 patients, split-face comparison) compared 70% GA (every 2 weeks, 3 sessions) to JS (every 2 weeks, 3 sessions).[20] Both GA and JS had similar effects and improved acne scores by ≥ 0.5 (50% each; RR, 1.00; 95% CI, 0.58-1.72). Self-reported improvements were equivalent for GA and JS (30.7% and 30.7%, respectively; RR, 1.00; 95% CI, 0.44-2.26), as were the choices for future treatment (50% and 30.7%, respectively; RR, 1.63; 95% CI, 0.81-3.65).

Adverse events

Erythema was common for both peels (no data available). However, JS induced scaling that negatively influenced patients' daily life (GA, 0%; JS, 36%; RR, 0.05; 95% CI, 0-0.86). Two patients could not tolerate the 70% GA treatment due to the development of acute eczema, crusting and oozing.

Comparison 10: TCA peel versus non-purpuric pulsed dye laser

One RCT (45 patients) compared 25% TCA peel (every 2 weeks, 6 sessions) to non-purpuric pulsed dye laser (every 2 weeks, 6 sessions).[21] The mean acne severity score was significantly improved, from baseline, for both TCA and laser therapy (MD

0.28; 95% CI, -0.33 to 0.89); the clinical response was equivalent for both agents (40% and 46.2%, respectively; RR, 0.87; 95% CI, 0.37-2.04). However, the mean remission period after treatment was significantly shorter for TCA than for laser therapy (MD -1.60 months, 95% CI -1.85 to -1.35).

Adverse events

The authors classified adverse events as follows: none; trace; mild; moderate; and severe. No severe adverse events were reported. Two patients (13%) in the TCA peel group and three (23.1%) in the laser therapy group reported moderate adverse events (RR, 0.58; 95% CI, 0.11-2.94). Mild adverse events were reported for six patients (40%) in the TCA peel group and five (38.5%) in the laser therapy group (RR, 1.04; 95% CI, 0.41-2.62). Both treatments were considered be well-tolerated.

Comparison 11: Lipohydroxy acid peel versus SA peel

One RCT (20 patients) compared lipohydroxy acid (LHA; 5% or 10%, every 2 weeks, 6 sessions) to SA (20% or 30%, every 2 weeks, 6 sessions).[9] Both LHA and SA reduced the number of non-inflammatory lesions (55.6% and 48.5%, respectively, p=0.878) and inflammatory lesions (no data available, p=0.111).

Adverse events

Both LHA and SA peels were well-tolerated. The global tolerance for the SA peel was better than that for the LHA peel when assessed by patients (no data available, p=0.028), but there was no difference when assessed by the investigator (no data available, p=0.546).

DISCUSSION

To the best of our knowledge, this is the first systematic review addressing chemical peels for treating acne vulgaris. Based on our analysis of the data presented in the 12 included RCTs, chemical peeling is an overall positive method of treating acne vulgaris. The following comparisons demonstrated the equivalence of peels for the treatment of acne vulgaris: TCA versus SA, GA versus AFA, SA versus PA, GA versus SA, GA versus JS, and LHA versus SA. Moreover, the combination of SA and MA provides a more effective peeling than GA. Furthermore, SA was found to be more effective than JS for the treatment of comedones, but less effective than phototherapy to treat pustules. The effectiveness of TCA is comparable to that of pulsed dye laser therapy, but the laser provided a longer period of remission.

All chemical peels evaluated were well-tolerated. The most common adverse events were: transient burning or sting sensations; post-peel erythema or scaling; and topical edema or dryness. A few patients reported acne flare-ups with the combination of SA and MA peel and with GA. Hyperpigmentation was a rare adverse event reported by patients treated with TCA, SA, and JS peels. Of note, this RCT did not have sufficient power to identify all adverse events, especially for rare adverse events, due to the limited sample size.[22]

The information provided in our review may assist dermatologists with selecting the most appropriate chemical peels to treat acne vulgaris. However, our findings should be considered with caution because the included RCTs were performed in different countries and recruited individuals of different ethnicities. The choice of chemical

peels should be individualized, based on patient's skin type, history of acne or other skin diseases and relevant treatments, and patient's expectations. For example, chemical peels, especially medium or deep peels, are unsuitable for those with a Fitzpatrick skin type V or VI, because these peels may cause dyspigmentation and scarring in these patients.[23 24] In fact, most included studies recruited patients with a Fitzpatrick skin type I through IV, although some studies did not report the skin type. In addition, most included studies focused on mild to moderate acne.

There is currently no consensus regarding the standardized regimen for chemical peeling, because the optimal concentration, treatment interval, and duration for different chemical peels remain unclear. In our review, the regimen of chemical peels varied significantly across studies. For example, the concentration of GA used in different RCTs varied from 10% to 70%, and the treatment durations varied from 6 to 24 weeks. Studies are warranted to compare different regimens of the same chemical peel to determine the optimal regimen for each peeling agent.

There is an emerging trend of using a combination of peeling agents because of the belief that better clinical results can be achieved while reducing the risk of adverse events. [3] As examples, Vitalize Peel® contains both SA and lactic acid, with Micropeel Plus® contains SA and GA for treating acne vulgaris. [5] However, we could not find any RCT to confirm the efficacy of the premixed chemical peeling agents for acne. In the future, more attention should be focused on these premixed formulating of chemical peels.

In this review, we surprisingly found that only one RCT [16] compared a chemical

peeling agent (GA) to placebo for acne vulgaris. However, more than 10 chemical peeling agents have been applied in the real world. Further well-designed RCTs are needed to compare other chemical peels to placebo. A network meta-analysis based on these RCTs should provide more valuable and robust evidence for clinical practice. Additionally, the outcome measurements were significantly different across the included RCTs, which made it difficult to compare or merge the results of different studies. Therefore, we suggest that the future version of the guideline of care for the management of acne vulgaris should make recommendations regarding the standard of outcome measurements. Our review has some limitations. First, all included studies were of very low-to-moderate methodological quality, with small sample sizes, which might have introduced bias. However, we evaluated for bias in each study. For example, most of the included RCTs did not describe the method of randomization. It is important to adhere to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement to avoid incomplete and inadequate reporting and to improve the quality of the evidence.[25] Second, this review did not investigate the effects of chemical peeling for acne scarring, although chemical peels are used clinically for this indication.[26] Finally, as previously discussed, the absence of a standardized peeling regimen limits the translation of our findings to clinical practice.

CONCLUSION

Implication for practice

Current evidence supports chemical peeling as a useful and well-tolerated intervention

for the treatment of mild-to-moderate acne vulgaris. Commonly used chemical peels have similar effects. However, there are limited data regarding premixed chemical peels for acne vulgaris.

Implications for research

Well-designed and well-reported RCTs are needed to provide high quality evidence to inform practice, particularly regarding the optimal formulation and regiment for chemical peeling agents. Comparisons with placebo or each other should be performed for various ethnic populations and skin types. In addition, standard outcome measurements for the management of acne vulgaris are needed.

ACKNOWLEDGEMENT

None.

COMPETING INTERESTS

All authors have not conflict of interest to declare.

CONTRIBUTORS

XC and LL designed the protocol. XC and MY searched the literature, extracted the data, and analysed the data. XC, SW, MY and LL interpreted the data and revised the manuscript.

FUNDING

This review was supported by a grant from the Sichuan Provincial Science and Technology Department (Grant number: 2017JY0277).

DISCLAIMER

The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report.

DATA SHARING STATEMENT

No additional data are available.

REFERENCES

1. Sathish D, Shayeda, Rao YM. Acne and its treatment options: a review. *Curr Drug Deliv* 2011;8(6):634-9.
2. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013;168(3):474-85. doi: 10.1111/bjd.12149
3. Kontochristopoulos G, Platsidaki E. Chemical peels in active acne and acne scars. *Clinics in Dermatology* 2017;35(2):179-82.
4. Salam A, Dadzie OE, Galadari H. Chemical peeling in ethnic skin: an update. *British Journal of Dermatology* 2013;169 Suppl 3:82-90.
5. Jackson A. Chemical peels. *Facial Plast Surg* 2014;30(1):26-34. doi: 10.1055/s-0033-1364220

6. Dreno B, Fischer TC, Perosino E, et al. Expert opinion: efficacy of superficial chemical peels in active acne management--what can we learn from the literature today? Evidence-based recommendations. *Journal of the European Academy of Dermatology & Venereology* 2011;25(6):695-704.

7. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74(5):945-73 e33. doi: 10.1016/j.jaad.2015.12.037

8. Ilknur T, Demirtasoglu M, Bicak MU, et al. Glycolic acid peels versus amino fruit acid peels for acne. *Journal of Cosmetic & Laser Therapy* 2010;12(5):242-5.

9. Levesque A, Hamzavi I, Seite S, et al. Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. *Journal of Cosmetic Dermatology* 2011;10(3):174-8.

10. Abdel Meguid AM, Elaziz Ahmed Attallah DA, Omar H. Trichloroacetic Acid Versus Salicylic Acid in the Treatment of Acne Vulgaris in Dark-Skinned Patients. *Dermatologic Surgery* 2015;41(12):1398-404.

11. Alba MN, Gerenutti M, Yoshida VM, et al. Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne vulgaris in teenagers. *Journal of Cosmetic & Laser Therapy* 2017;19(1):49-53.

12. Bae BG, Park CO, Shin H, et al. Salicylic acid peels versus Jessner's solution for acne vulgaris: a comparative study. *Dermatologic Surgery* 2013;39(2):248-53.

13. Dayal S, Amrani A, Sahu P, et al. Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. *J Cosmet Dermatol* 2017;16(1):43-51. doi: 10.1111/jocd.12266

14. ElRefaei AM, Abdel Salam HA, Sorour NE. Salicylic-mandelic acid versus glycolic acid peels in Egyptian patients with acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society* 2015;12(3):196-202.

15. Jaffary F FGSSHSM. Comparison the effectiveness of pyruvic acid 50% and salicylic acid 30% in the treatment of acne. *Journal of research in medical sciences* 2016;21(2)

16. Kaminaka C, Uede M, Matsunaka H, et al. Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. *Dermatologic Surgery* 2014;40(3):314-22.

17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535. doi: 10.1136/bmj.b2535

18. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane

Collaboration; 2011 [Available from: www.handbook.cochrane.org.

19. Kessler E, Flanagan K, Chia C, et al. Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. *Dermatologic Surgery* 2008;34(1):45-50; discussion 51.

20. Kim SW, Moon SE, Kim JA, et al. Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. *Dermatologic Surgery* 1999;25(4):270-3.

21. Leheta TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. *Journal of Cosmetic & Laser Therapy* 2009;11(2):118-24.

22. Wahab IA, Pratt NL, Kalisch LM, et al. The detection of adverse events in randomized clinical trials: can we really say new medicines are safe? *Current drug safety* 2013;8(2):104-13. [published Online First: 2013/05/30]

23. Been MJ, Mangat DS. Laser and face peel procedures in non-Caucasians. *Facial Plastic Surgery Clinics of North America* 2014;22(3):447-52.

24. Handog EB, Datuin MS, Singzon IA. Chemical peels for acne and acne scars in asians: evidence based review. *Journal of Cutaneous & Aestheic Surgery* 2012;5(4):239-46.

25. Boutron I, Altman DG, Moher D, et al. CONSORT Statement for

Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med* 2017;167(1):40-47. doi: 10.7326/M17-0046

26. Abdel Hay R, Shalaby K, Zaher H, et al. Interventions for acne scars. *Cochrane Database of Systematic Reviews* 2016(pagination)

FIGURE LEGEND

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) diagram of the study flow.

Figure 2. Risk of bias summary for each study.

Figure 3. Risk of bias summary graph for all included studies.

SUPPLEMENTARY FILES

Supplementary Table 1. The search strategies for MEDLINE, EMBASE and CENTRAL via OvidSP.

Supplementary Table 2. Reasons for study exclusion

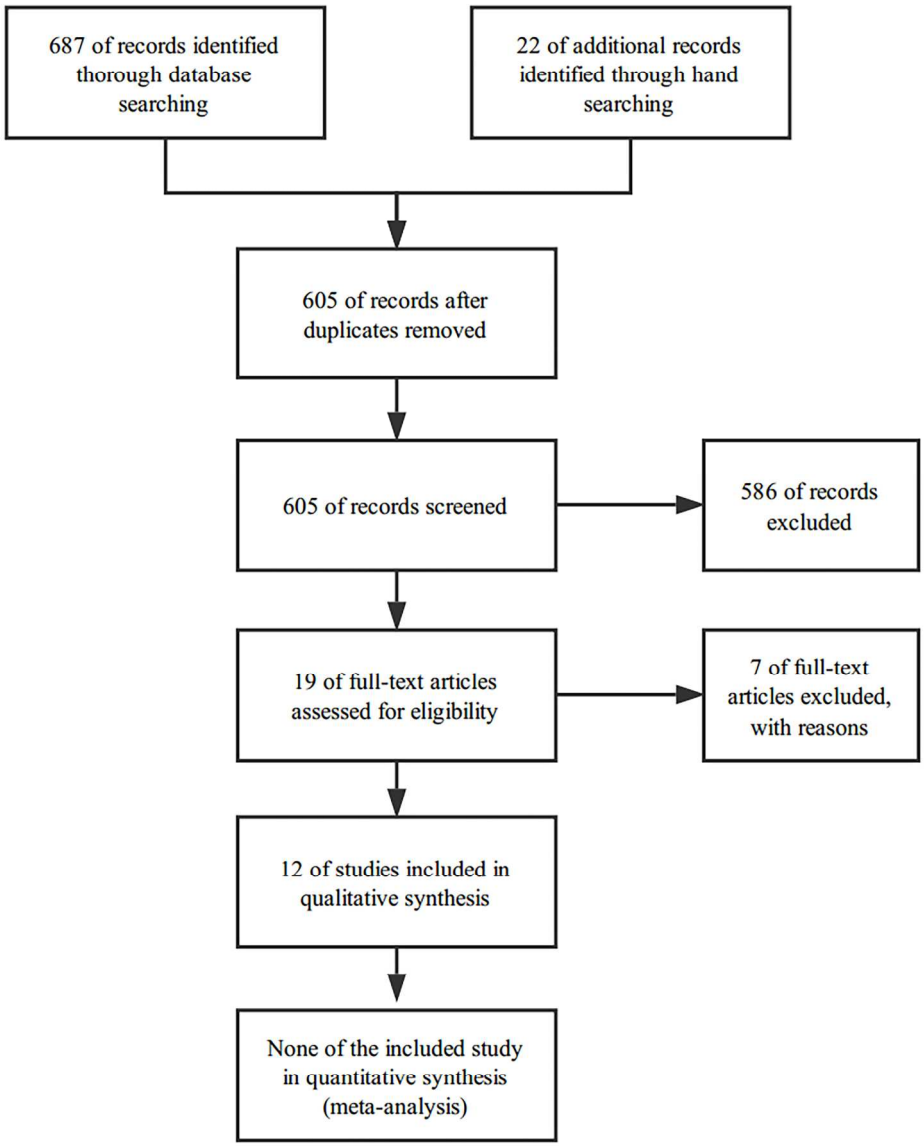

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) diagram of the study flow.

213x260mm (300 x 300 DPI)

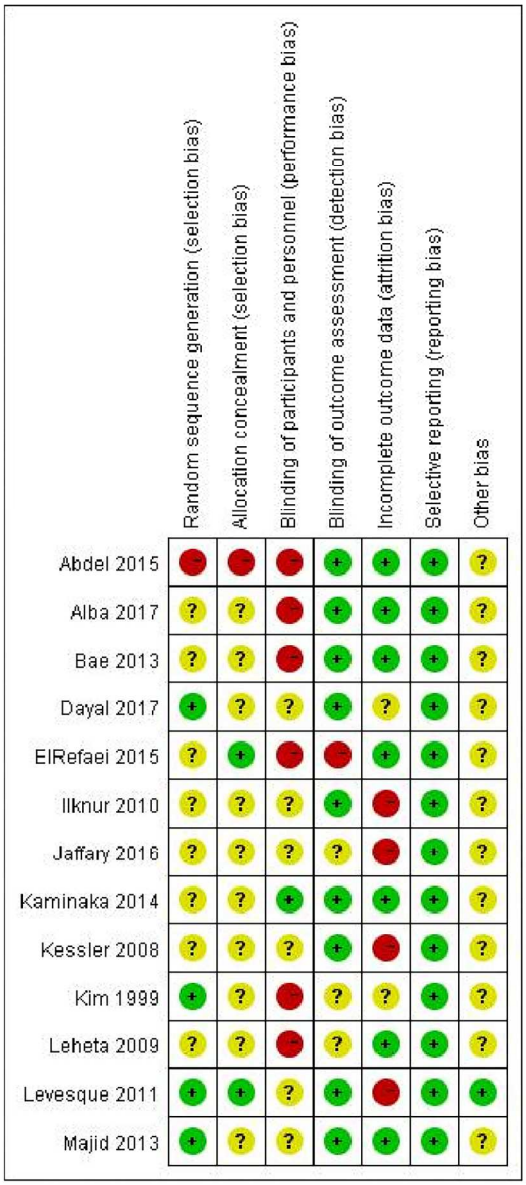

Figure 2. Risk of bias summary for each study.

138x297mm (300 x 300 DPI)

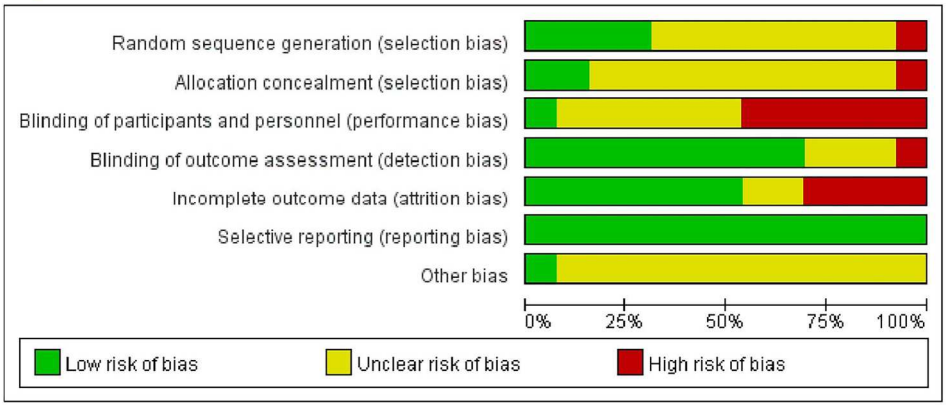

Figure 3. Risk of bias summary graph of all included studies.

209x87mm (300 x 300 DPI)

Supplementary Table 1. Search strategies for searching MEDLINE, EMBASE, and CENTRAL via OvidSP

No.	Searches
1	(chemical adj (peel* or resurface*).ab,kw,ti.
2	((hydroxy or glycolic or lactic or malic or citric or tartaric or salicylic or trichloroacetic or pyruvic or lipohydroxy or salicylic-mandelic or "amino fruit") adj acid*).ab,kw,ti.
3	("Jessner's solution" or "Jessner's solutions").ab,kw,ti.
4	(resorcinol* or phenol*).ab,kw,ti.
5	acne.ab,kw,ti.
6	exp *Acne Vulgaris/
7	1 or 2 or 3 or 4
8	5 or 6
9	7 and 8
10	remove duplicates from 9

Supplementary Table 2. Reasons for study exclusion

Studies	Reason for exclusion
Garg 2009 [1]	This study is not an RCT.
Kim 2015 [2]	This RCT compared alpha hydroxy acids plus an additional physical treatment with alpha hydroxy acids alone.
Lee 2006 [3]	This study is not an RCT.
Lekakh 2015 [4]	This study compared chemical peel and the combination of laser and chemical peel.
Nofal 2014 [5]	This study appears to be not an RCT because of the significant difference between the method section and the abstract about the randomization. And there is no reply from the authors to clarify this inconsistency.
Sharad 2011 [6]	This study is not an RCT
Wang 1997 [7]	This study is not an RCT

RCT: randomized controlled trial.

References of the excluded studies:

1. Garg VK, Sinha S , Sarkar R. Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: a comparative study. Dermatologic Surgery 2009;35:59-65.

2. Kim SJ, Baek JH, Koh JS, Bae MI, Lee SJ , Shin MK. The effect of physically applied

alpha hydroxyl acids on the skin pore and comedone. International Journal of Cosmetic Science 2015;37:519-25.

3. Lee SH, Huh CH, Park KC , Youn SW. Effects of repetitive superficial chemical peels on facial sebum secretion in acne patients. Journal of the European Academy of Dermatology & Venereology 2006;20:964-8.

4. Lekakh O, Mahoney AM, Novice K, Kamalpour J, Sadeghian A, Mondo D et al. Treatment of Acne Vulgaris With Salicylic Acid Chemical Peel and Pulsed Dye Laser: A Split Face, Rater-Blinded, Randomized Controlled Trial. Journal of Lasers in Medical Sciences 2015;6:167-70.

5. Nofal E, Helmy A, Nofal A, Alakad R , Nasr M. Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: a comparative study. Dermatologic Surgery 2014;40:864-73.

6. Sharad J. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. Journal of Cosmetic Dermatology 2011;10:317-23.

7. Wang CM, Huang CL, Hu CT , Chan HL. The effect of glycolic acid on the treatment of acne in Asian skin. Dermatologic Surgery 1997;23:23-9.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not necessary

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not necessary
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Meta-analysis is not possible to be performed.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not necessary
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019607.R2
Article Type:	Research
Date Submitted by the Author:	14-Mar-2018
Complete List of Authors:	Chen, Xiaomei; Sichuan University West China Hospital, Department of Dermatology & Venereology Wang, Sheng; Sichuan University West China Hospital, Department of Dermatology & Venereology Yang, Ming; The Center of Gerontology and Geriatrics; Li, Li; Sichuan University West China Hospital, Department of Dermatology & Venereology
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Evidence based practice, Infectious diseases
Keywords:	chemical peeling, acne vulgaris, systematic review, treatment, comedone, papule

Title Page

Title

Chemical peels for acne vulgaris: a systematic review of randomized controlled trials

Authors

Xiaomei Chen M.D., Sheng Wang M.D., Ming Yang M.D., Li Li M.D.

Affiliations and locations of all authors

Xiaomei Chen: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Sheng Wang: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Ming Yang: The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China

Li Li: Department of Dermatology & Venereology, West China Hospital, Sichuan University, Chengdu, China

Corresponding author

Li Li, M.D.: Department of Dermatology & Venereology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. Telephone: +86 28 85423315; Fax: +86 28 85423315; Email:

hxskincos2017@qq.com

Word counts

Manuscript: 4437 words

Abstract

Objective: We evaluated current evidence from randomized controlled trials (RCTs) regarding the effectiveness of chemical peeling for treating acne vulgaris.

Methods: Standard Cochrane methodological procedures were used. We searched MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE via OvidSP through April 2017. Reviewers independently assessed eligibility, risk of bias, and extracted data.

Results: Twelve RCTs (387 participants) were included. Effectiveness was not significantly different: trichloroacetic acid versus salicylic acid (SA) (percentage of total improvement: relative risk [RR] 0.89; 95% confidence interval [CI], 0.73-1.10), glycolic acid (GA) versus amino fruit acid (the reduction of inflammatory lesions: mean difference [MD], 0.20; 95% CI, -3.03 to 3.43), SA versus pyruvic acid (excellent or good improvement: RR, 1.11; 95% CI, 0.73-1.69), GA versus SA (good or fair improvement: RR, 1.00; 95% CI, 0.85-1.18), GA versus Jessner's solution (JS) (self-reported improvements: RR, 1.00; 95% CI, 0.44-2.26), and lipohydroxy acid versus SA (reduction of noninflammatory lesions: 55.6% vs. 48.5%, p=0.878).

Combined SA and mandelic acid peeling was superior to GA peeling (percentage of improvement in total acne score: 85.3% vs. 68.5%, p<0.001). GA peeling was superior to placebo (excellent or good improvement: RR, 2.30; 95% CI, 1.40-3.77). SA peeling may be superior to JS peeling for comedones (reduction of comedones: 53.4% vs. 26.3%, p=0.001) but less effective than phototherapy for pustules (number of pustules: MD, -7.00; 95% CI, -10.84 to -3.16).

Limitations: The methodological quality of the included RCTs was very low to moderate. Meta-analysis was not possible due to the significant clinical heterogeneity across studies.

Conclusion: Commonly used chemical peels appear to be similarly effective for mild-to-moderate acne vulgaris and well tolerated. However, based on current limited evidence, a robust conclusion cannot be drawn regarding any definitive superiority or equality among the currently used chemical peels. Well-designed RCTs are needed to identify optimal regimens.

Keywords: chemical peeling; acne vulgaris; systematic review; treatment; comedone; papule; pustule

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA) protocols and Cochrane methodological procedures.
- Twelve RCTs with 387 participants were included.
- The methodological quality of the included RCTs was very low to moderate.
- A meta-analysis cannot be performed due to the significant heterogeneity across

the RCTs.

INTRODUCTION

Acne is one of the most common skin disorders and is prevalent in most ethnic populations.[1] Acne affects 85% to 90% of adolescents, and may persist into adulthood.[2 3] Acne vulgaris can negatively affect an individual's appearance and self-esteem, thereby causing anxiety, depression, poor quality of life, and even suicidal thought.[1 2] Skin lesions of acne vulgaris are classified as either noninflammatory (comedones) or inflammatory (papules, pustules, nodules, and cysts). Acne vulgaris treatments include systemic therapies (oral antibiotics and retinoid), topical therapies (benzoyl peroxide) and physical modalities (laser therapy and chemical peeling).

Chemical peeling is a skin resurfacing procedure commonly used for facial rejuvenation and esthetics.[3] It causes a manageable injury to the skin, thus resulting in subsequent regeneration of a new epidermal layer of the dermal tissues.[4] The injury depth is determined by the concentration of acid used, and by the type of vehicle, buffering, and duration of skin contact. Therefore, chemical peels are classified as superficial (destroying the epidermis), moderate (destroying the papillary dermis and upper reticular dermis), or deep (destroying part or all of the mid-reticular dermis).[5] Although often used to treat acne, chemical peeling is also widely used as a cosmetic treatment for melasma, photoaging, and lentigines.[5] Superficial peels are generally used for acne vulgaris, whereas deep peels are used to treat acne scars. Commonly

used agents for chemical peels are summarized in Table 1.

Table 1. The abbreviations of commonly used chemical peels for acne vulgaris [4-9]

Chemical peels	Abbreviations
α-Hydroxy acid	AHA
Amino fruit acid	AFA
Glycolic acid	GA
Mandelic acid	MA
Tartaric acid	TA
β-Hydroxy acid	BHA
Salicylic acid	SA
Azelaic acid	AZA
Lipohydroxy acid	LHA
Jessner's solution*	JS
Pyruvic acid	PA
Retinoic acid	RA
Trichloroacetic acid	TCA

*Jessner's solution is a premixed formula containing 14% salicylic acid, 14% lactic acid, and 14% resorcinol.

The exact pathogenesis of acne vulgaris remains unclear. However, the proliferation of *Propionibacterium acnes*, increased levels of inflammatory cytokines and sebum production, and follicular hyperkeratinization are involved.[3] Chemical peels have antibacterial, anti-inflammatory, keratolytic, and comedolytic effects, and they can reduce sebum production. Therefore, chemical peels have been widely used to treat acne vulgaris, either as a supplementary therapy or as a maintenance therapy.[3 5 8]

Despite their wide application, evidence regarding the effectiveness of chemical peels in the treatment of acne vulgaris is limited. A 2016 recommendation for the treatment of acne vulgaris indicated that chemical peels were supported by level B evidence, namely, "inconsistent or limited-quality patient-oriented evidence".[10] This

recommendation was based on the evaluation of two trials [11 12] and a previously published guideline [8], and it only included research from the PubMed and the Cochrane Library databases, from May 2006 to September 2014. Therefore, potential evidence from other important medical databases was possibly omitted. In addition, new randomized controlled trials (RCTs) were performed after September 2014.[12-19] Thus, we performed a systematic review to summarize current evidence regarding the effectiveness of chemical peeling for acne vulgaris and to evaluate the validity of the aforementioned recommendations.

METHODS

Systematic search of the literature

This review was performed according to the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA)[20] and the Standard Cochrane methodological procedures.[21] The following databases were searched until April 25, 2017, using the strategy summarized in Supplementary Table 1: MEDLINE via OvidSP (from 1946), EMBASE via OvidSP (from 1974), and the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 4.

We also hand-searched all bibliographies of the included and excluded studies and previous systematic reviews to identify further relevant trials.

Inclusion and exclusion criteria

We included all RCTs addressing any chemical peel (compared to placebo or any

other treatment) for the treatment of acne vulgaris in any study population. Studies that recruited patients with sequelae of acne, such as post-inflammatory dyschromia or scarring; evaluated the combined effects of chemical agents and other therapies, such as laser therapy; were quasi-RCTs; and were not published in English were excluded.

Selection of studies

Two authors (X.C. and M.Y.) independently reviewed the titles and abstracts identified from the searches and selected possible relevant studies. After reviewing the full text of these studies, the two authors independently decided on which studies to include and exclude and documented the reasons for exclusion. Any discrepancy in the selection was resolved through discussion.

Data extraction

Two authors (X.C. and M.Y.) independently extracted the information from the included studies using the "characteristics of included studies form" recommended by the Cochrane Handbook for Systematic Review of Interventions.[21] Another author (W.S.) verified and compared the data extraction forms.

Assessment of the risk of bias in included trials

Two authors (X.C. and M.Y.) independently evaluated the risk of bias in the included trials using the methods recommended by the Cochrane Handbook for Systematic Review of Interventions.[21] Discrepancies were resolved through discussion. The

Cochrane risk of bias for each included trial was classified as low, high, or unclear.

Measure of treatment effects

Dichotomous outcomes (such as the percentage of meaningful improvement in the total number of lesions) were reported, when possible, as risk ratios (RRs), with the associated 95% confidence intervals (CIs). Continuous outcomes (such as the number of inflammatory lesions) were reported as the mean difference (MD), with the associated 95% CI.

Heterogeneity and data synthesis

Significant clinical heterogeneity across the included RCTs was identified. Specifically, the skin type of participants, interventions (e.g., the type, concentration, and regimen of chemical peeling agents), and outcome measurements were all significantly different across the included RCTs. Therefore, it was not possible to merge data from different trials to perform a meta-analysis.

Patient and public involvement

Patients and public were not involved.

RESULTS

Description of studies

After removing duplicates, we identified 605 articles during the initial search. Of these, 586 were discarded after screening the titles and abstracts, leaving 19 studies

for full review. Another seven of the 19 studies were excluded after this review. The reasons for exclusion are summarized in Supplementary Table 2. Our final analysis included 12 RCTs, providing data from 387 participants. The PRISMA diagram for study selection is presented in Figure 1. Relevant characteristics of the included RCTs are summarized in Table 2.

Table 2. Summary of relevant characteristics of included studies

Studies	Publication year	Study design	Country	Sample size	Women (%)	Fitzpatrick skin type	Acne severity	Interventions	Main outcomes	Follow-up (weeks)
Abdel et al.[13]	2015	Single-center, double-blind, split-face RCT	Egypt	20	85	III, IV, V	Mild to moderate	25% TCA versus 30% SA (in hydroethanolic vehicle)	✧ Percentage of total/ good/ fair/ poor improvement in total lesions ✧ Percentage of total/ good/ fair/ poor improvement in noninflammatory lesions ✧ Percentage of total/ good/ fair/ poor improvement in inflammatory lesions ✧ Reduction of lesion counts ✧ Adverse events	10
Alba et al.[14]	2017	Single-center, single-blind RCT	Brazil	22	41	II, III, IV, VI	Mild to moderate	10% SA (in cream-gel) versus phototherapy	✧ Comedone counts ✧ Papule counts ✧ Pustule counts	10
Bae et al.[15]	2013	Single-center, single-blind, split-face RCT	Korea	13	0	III or IV	Mild to moderate	30% SA versus JS	✧ Number of noninflammatory lesions ✧ Number of inflammatory lesions ✧ Self-reported good/ moderate/ mild/ no improvement in all lesions ✧ Adverse events	8
Dayal et al. [16]	2017	Single-center, single-blind RCT	India	40	35	N/A	Mild to moderate	30% SA versus JS	✧ Comedone counts ✧ Overall percentage decrease in mean comedone counts ✧ Papule counts ✧ Overall percentage decrease in mean papule counts ✧ Pustule counts	12

EIRefaei et al. [17]	2015	Single-center, open-label RCT	Egypt	40	80	I, II, III, IV	Mild to very severe	20% SA + 10% MA (in ethyl alcohol vehicle) versus 35% GA (in distilled water)	✧ Overall percentage decrease in mean pustule counts ✧ MAS ✧ Percentage decrease in mean MAS ✧ Percentage of good/ fair/ poor response ✧ Adverse events ✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of improvement in comedones/ papules/ pustules/ the total acne score ✧ Adverse events	20
Ilknur et al. [11]	2010	Single-center, single-blind, split-face RCT	Turkey	30	N/A	II, III	Mild to moderate	GA (from 20% to 70%) versus AFA (from 20% to 60%)	✧ Noninflammatory lesion counts ✧ Inflammatory lesion counts ✧ Patients' choice for future treatment ✧ Adverse events	24
Jaffary et al. [18]	2016	Multi-center, single-blind RCT	Iran	86	92	N/A	Mild to moderate	30% SA (in alcohol vehicle) versus 50% PA (in hydro	✧ Comedone counts ✧ Papule counts ✧ Pustule counts ✧ Percentage of excellent/ good/ fair/ poor improvement of all lesions ✧ Acne severity index (ASI) ✧ Percentage of patient satisfaction ✧ Adverse events	8

								alcoholic vehicle)		
Kaminaka et al. [19]	2014	Single-center, double-blind, split-face RCT	Japan	25	64	N/A	Moderate to severe	40% GA versus Placebo (hydrochloric acid in polyethylene glycol vehicle)	✧ Noninflammatory lesion counts ✧ Inflammatory lesion counts ✧ Total lesion counts ✧ Percentage of excellent/ good/ fair/ bad improvement in all lesions ✧ Bioengineering measurements ✧ Adverse events	10
Kessler et al. [22]	2008	Single-center, double-blind, split-face RCT	United States	20	65	N/A	Mild to moderate	30% GA versus 30% SA	✧ Mean number of all lesions ✧ Reduction of all lesions ✧ Percentage of good/ fair/ poor improvement in all lesions ✧ Self-reported overall improvement ✧ Adverse events	20
Kim et al. [23]	1999	Single-center, single-blind, split-face RCT	Korea	26	84.6	III, IV	Mild to moderate	70% GA versus JS (resorcinol, salicylic acid, lactic acid in ethanol)	✧ Percentage of patients who achieved improvement in acne scores of 0.5 or more ✧ Self-reported overall improvement ✧ Patients' choice for future treatment ✧ Adverse events	8
Leheta et al. [24]	2009	Single-center, single-blind, RCT	Egypt	45	N/A	II, III, IV	Mild to moderate	20% TCA versus PDL	✧ Acne severity score ✧ Mean remission period ✧ Percentage of marked/ moderate response ✧ Self-reported cost-effectiveness ratio ✧ Adverse events	48

Levesque et al. [12]	2011	Single-center, open-label, split-face RCT	United States	20	95	N/A	N/A	LHA (5% or 10%) versus SA (20% or 30%)	✧ Reduction of noninflammatory lesions ✧ Inflammatory lesion counts ✧ Global acne assessment ✧ Adverse events	14

AFA: amino fruit acid; AZA: azelaic acid; GA: glycolic acid; JS: Jessner's solution; LHA: lipohydroxy acid; MA: mandelic acid; N/A: not available; PA: pyruvic acid; PDL: pulsed dye laser; RCT: randomized controlled trial; SA: salicylic acid: TCA: trichloroacetic acid.

Risk of bias in included studies

The methodological quality of included RCTs was generally low to moderate; however, in some cases, it was very low. The risk of bias in each included study is shown in Figure 2, with the percentage of each risk of bias item across studies summarized in Figure 3.

Effects of interventions

Due to significant differences across studies with regard to interventions (different chemical peels and regimens), outcomes, and follow-up durations, data from the different studies could not be combined to perform a meta-analysis. We identified a total of eight different chemical peels and grouped the data into 11 comparisons.

Comparison 1: Trichloroacetic acid peel versus salicylic acid peel

One RCT (20 participants, split-face comparison) compared 25% trichloroacetic acid (TCA; every 2 weeks, 4 sessions) to 30% salicylic acid (SA; every 2 weeks, 4 sessions) for the treatment of mild-to-moderate acne vulgaris. Skin lesions significantly improved, from baseline, in both treatment groups, with no significant difference between TCA and SA in terms of the percentage of total improvement for all lesions (85% vs. 95%; RR 0.89; 95% CI, 0.73-1.10), for noninflammatory lesions (80% vs. 70%; RR 1.14; 95% CI, 0.80-1.64), and for inflammatory lesions (80% vs. 85%; RR 0.94; 95% CI, 0.71-1.25).[13]

Adverse events

No adverse event was identified for the SA peel. For the TCA peel, four patients (20%) reported hyperpigmentation that lasted for 3 to 4 weeks.[13]

Comparison 2: SA peel versus phototherapy

One RCT (22 participants) compared 10% SA (once every week, 10 sessions) to phototherapy (once every week, 10 sessions). Both interventions significantly improved acne lesions, with no significant difference between the two interventions in terms of the reduction in the number of comedones (MD, 2.00; 95% CI, -3.67 to 7.67) and papules (MD, -1.00; 95% CI, -4.40 to 2.40). However, the SA peel did not reduce the number of pustules to the same extent as phototherapy (MD, -7.00; 95% CI, -10.84 to -3.16).[14]

Adverse events

No information regarding adverse effects was reported.[14]

Comparison 3: SA peel versus Jessner's solution peel

Two RCTs compared SA to Jessner's solution (JS) peels.[15 16] Because of significant differences in the treatment regimen, measured outcomes, and follow-up duration, data from these two studies could not be combined for analysis.

One RCT (13 patients, split-face comparison) compared 30% SA (every 2 weeks, 3 sessions) to JS (every 2 weeks, 3 sessions).[15] The authors stated that SA "seemed to be more effective than" JS for the treatment of noninflammatory lesions. However, relevant data supporting this conclusion were not clearly described. Furthermore, the authors reported that both SA and JS were effective in reducing inflammatory lesions;

however, they did not compare the effects of SA and JS on this outcome.

Another RCT (40 patients) also compared 30% SA (every 2 weeks, 6 sessions) to JS (every 2 weeks, 6 sessions).[16] SA was superior to JS in terms of overall percentage decrease in the mean number of comedones (53.4% and 26.3%, respectively, p=0.001), with equivalent outcomes for papules (71.0% and 61.5%, respectively, p=0.870) and pustules (70.3% and 76.7%, respectively, p=0.570). The proportional decreases in the mean Michaelson acne score (MAS), before and after treatment, were greater for SA than for JS (60.4% and 34.1%, respectively, p=0.002).

Adverse events

Initial burning sensations, post-peeling erythema and mild scaling were common symptoms that were comparable for the SA and JS groups.[16] One patient reported intense scaling on the side that was treated with SA.[15] There was no report of hyperpigmentation.

Dayal et al. reported that SA and JS were both well-tolerated, although SA induced more burning and stinging sensation (65% and 45%, respectively; RR 2.27; 95% CI, 0.64-8.11; nonsignificant between-group difference).[16] However, post-peeling erythema was less common in the SA group than in the JS group (20% and 30%, respectively; RR 0.58; 95% CI 0.14-2.50; nonsignificant between-group difference). Hyperpigmentation was rare in both groups (5% and 15%, respectively; RR 0.30; 95% CI, 0.30-3.15).

Comparison 4: SA plus mandelic acid peel versus glycolic acid peel

One RCT (40 patients) compared 20% SA plus 10% mandelic acid (MA; every 2

weeks, 6 sessions) to 35% glycolic acid (GA; every 2 weeks, 6 sessions). [17] The combination of SA and MA was superior to GA in terms of the percentage of improvement, from baseline, in comedones (90.2% and 35.9%, respectively, p<0.05), papules (81.7% and 77.8%, respectively, p=0.006), and pustules (85.4% and 75.7%, respectively, p<0.001), as well as in the total acne score (85.3% and 68.5%, respectively, p<0.001).

Adverse events

There was no significant difference between these two intervention groups in terms of burning or stinging sensations (20% and 10%, respectively; RR, 2.00; 95% CI, 0.41-9.71), skin dryness (15% and 10%, respectively; RR, 1.50; 95% CI, 0.28-8.04), and acne flare-up (10% each; RR, 1.00; 95% CI, 0.16-6.42). However, the combination of SA and MA induced more visible desquamation than GA (80% and 40%, respectively; RR, 2.00; 95% CI, 1.12-3.57).

Comparison 5: GA peel versus amino fruit acid peel

One RCT (30 patients, split-face comparison) compared GA (at concentrations of 20%, 35%, 50%, and 70%; every 2 weeks, 12 sessions) to amino fruit acid (AFA) (at similar concentrations of 20%, 30%, 40%, 50%, and 60%; every 2 weeks, 12 sessions). [11] Both peeling agents significantly improved acne lesions and had comparable effectiveness in reducing the number of noninflammatory lesion counts (MD, 2.35; 95% CI, -18.66 to 23.36), the reduction of inflammatory lesions (MD, 0.20; 95% CI, -3.03 to 3.43), and patient's choice of future treatment (GA, 45.8%; AFA, 54.2%; RR, 0.85; 95% CI, 0.48-1.50).

Adverse events

All patients reported erythema at least once for both peels during the follow-up period. Edema was more common for GA than for AFA (91.7% and 50%, respectively; RR, 1.83; 95% CI, 1.21-2.78).[11] The incidence of frosting was comparable for both GA and AFA peels (29.2% vs. 16.7%, respectively; RR, 1.75; 95% CI, 0.59-5.21). Of note, all patients reported discomfort that negatively affected daily life with the GA peel.

Comparison 6: SA peel versus pyruvic acid peel

One RCT (86 patients) compared 30% SA (every 2 weeks, five sessions) to 50% pyruvic acid (PA; every 2 weeks, 5 sessions).[18] The two peels had similar effects for reducing comedones (MD, 7.45; 95% CI, -18.46 to 33.36), papules (MD, -0.20; 95% CI, -5.36 to 4.96) and pustules (MD, -1.03; 95% CI, -2.01 to 0.05). The achievement of an excellent or good improvement in all lesions was comparable for both SA and PA peels (66.7% and 60%, respectively; RR, 1.11; 95% CI, 0.73-1.69).[18]

Adverse events

Burning sensations were very common (>85%) for both peels. The incidences of scaling, erythema and itching were also reported to be comparable (with no data presented). Hyperpigmentation was rare and comparable for the SA and PA peels (11.1% and 8%, respectively; RR, 1.39; 95% CI, 0.25-7.64).

Comparison 7: GA peel versus placebo

One RCT (25 patients, split-face comparison) compared 40% GA (every 2 weeks, 5 sessions) to a placebo (every 2 weeks, 5 sessions).[19] GA was significantly superior to

the placebo for reducing the number of noninflammatory lesions (no data available, p<0.01), inflammatory lesions (no data available, p<0.01) and total lesions (no data available, p<0.01).[19] The achievement of excellent or good improvement in all lesions was also superior for GA than for the placebo (92% vs. 40%, respectively; RR, 2.30; 95% CI, 1.40-3.77).

Adverse events

The authors reported that most patients experienced "transient post-treatment mild erythema that lasted a few minutes at most", but no supporting data were presented.[19] Mild dryness was less common in the GA group than in the placebo group (28% and 100%, respectively; RR, 0.29; 95% CI, 0.16-0.54); however, the incidence of scaling was comparable between the groups (16% and 12%, respectively; RR, 1.33; 95% CI, 0.33-5.38). A flare-up rate of 12% was reported for GA, whereas no flare-up was reported for the placebo, although this difference was not significant (RR, 7.00; 95% CI, 0.38-128.87).

Comparison 8: GA peel versus SA peel

One RCT (20 patients, split-face comparison) compared 30% GA (every 2 weeks, 6 sessions) to 30% SA (every 2 weeks, 6 sessions).[22] Good or fair improvement in the total number of lesions at 1 month post-treatment was achieved with both GA and SA (94.1% each; RR, 1.00; 95% CI, 0.85-1.18). However, the mean number of all lesions was significantly higher on the GA-treated side than on the SA-treated side after a 2-month follow-up with no treatment (no data available, p<0.01). In terms of the patients' self-assessments, 41% of patients preferred GA, whereas35% preferred SA

(RR, 1.17; 95% CI, 0.49-2.75).

Adverse events

The authors reported that both GA and SA were safe and well tolerated, with no difference in adverse events rates between the two peels. The most common adverse events were scaling, peeling, and erythema (no data available).

Comparison 9: GA peel versus JS peel

One RCT (26 patients, split-face comparison) compared 70% GA (every 2 weeks, 3 sessions) to JS (every 2 weeks, 3 sessions).[23] Both GA and JS had similar effects and improved acne scores by ≥ 0.5 (50% each; RR, 1.00; 95% CI, 0.58-1.72). Self-reported improvements were equivalent for GA and JS (30.7% and 30.7%, respectively; RR, 1.00; 95% CI, 0.44-2.26), as were the choices for future treatment (50% and 30.7%, respectively; RR, 1.63; 95% CI, 0.81-3.65).

Adverse events

Erythema was common for both peels (no data available). However, JS induced scaling that negatively influenced patients' daily life (GA, 0%; JS, 36%; RR, 0.05; 95% CI, 0-0.86). Two patients could not tolerate the 70% GA treatment due to the development of acute eczema, crusting, and oozing.

Comparison 10: TCA peel versus non-purpuric pulsed dye laser

One RCT (45 patients) compared 25% TCA peel (every 2 weeks, 6 sessions) to non-purpuric pulsed dye laser (every 2 weeks, 6 sessions).[24] The mean acne severity score was significantly improved, from baseline, for both TCA and laser therapy (MD

0.28; 95% CI, -0.33 to 0.89); the clinical response was equivalent for both agents (40% and 46.2%, respectively; RR, 0.87; 95% CI, 0.37-2.04). However, the mean remission period after treatment was significantly shorter for TCA than for laser therapy (MD -1.60 months; 95% CI, -1.85 to -1.35).

Adverse events

The authors classified adverse events as follows: none, trace, mild, moderate, and severe. No severe adverse events were reported. Two patients (13%) in the TCA peel group and three (23.1%) in the laser therapy group reported moderate adverse events (RR, 0.58; 95% CI, 0.11-2.94). Mild adverse events were reported for six patients (40%) in the TCA peel group and five (38.5%) in the laser therapy group (RR, 1.04; 95% CI, 0.41-2.62). Both treatments were considered to be well tolerated.

Comparison 11: Lipohydroxy acid peel versus SA peel

One RCT (20 patients) compared lipohydroxy acid (LHA; 5% or 10%, every 2 weeks, 6 sessions) to SA (20% or 30%, every 2 weeks, 6 sessions).[12] Both LHA and SA reduced the number of noninflammatory lesions (55.6% and 48.5%, respectively, p=0.878) and inflammatory lesions (no data available, p=0.111).

Adverse events

Both LHA and SA peels were well-tolerated. The global tolerance for the SA peel was better than that for the LHA peel upon patient assessment (no data available, p=0.028), but there was no difference investigator assessment (no data available, p=0.546).

DISCUSSION

To the best of our knowledge, this is the first systematic review addressing chemical peels for treating acne vulgaris. Based on our analysis of the data presented in the 12 included RCTs, chemical peeling is an overall positive method of treating acne vulgaris. The following comparisons demonstrated the equivalence of peels for the treatment of acne vulgaris: TCA vs. SA, GA vs. AFA, SA vs. PA, GA vs. SA, GA vs. JS, and LHA vs. SA. Moreover, the combination of SA and MA results in a more effective peeling than GA. Furthermore, SA was found to be more effective than JS for the treatment of comedones, but less effective than phototherapy in treating pustules. The effectiveness of TCA is comparable to that of pulsed dye laser therapy, but the laser provided a longer period of remission.

All chemical peels evaluated were well-tolerated. The most common adverse events were as follows: transient burning or stinging sensations, post-peeling erythema or scaling, and topical edema or dryness. A few patients reported acne flare-ups with the combination of SA and MA peel and with GA alone. Hyperpigmentation was a rare adverse event reported by patients treated with TCA, SA, and JS peels. Of note, this RCT did not have sufficient power to identify all adverse events, especially rare adverse events, due to the limited sample size.[25]

The information provided in our review may assist dermatologists with selecting the most appropriate chemical peels to treat acne vulgaris. However, our findings should be considered with caution because the included RCTs were performed in different countries and recruited individuals of different ethnicities. The choice of chemical

peels should be individualized, based on the patient's skin type, history of acne or other skin diseases and relevant treatments, and expectations. For example, chemical peels, especially medium or deep peels, are unsuitable for those with a Fitzpatrick skin type V or VI, because these peels may cause dyspigmentation and scarring in these patients.[26 27] In fact, most included studies recruited patients with a Fitzpatrick skin type I through IV, although some studies did not report the skin type. In addition, most included studies focused on mild-to-moderate acne.

There is currently no consensus regarding the standardized regimen for chemical peeling, because the optimal concentration, treatment interval, and duration for different chemical peels remain unclear. In our review, the regimen of chemical peels varied significantly across studies. For example, the concentration of GA used in different RCTs varied from 10% to 70%, and the treatment durations varied from 6 to 24 weeks. Studies are warranted to compare different regimens of the same chemical peel in order to determine the optimal regimen for each peeling agent.

There is an emerging trend of using a combination of peeling agents because of the belief that better clinical results can be achieved while reducing the risk of adverse events. [3] For instance, Vitalize Peel® contains both SA and lactic acid, while Micropeel Plus® contains SA and GA for treating acne vulgaris. [5] However, we could not find any RCT to confirm the efficacy of the premixed chemical peeling agents for acne. In the future, more attention should be focused on these premixed formulations of chemical peels.

In this review, we surprisingly found that only one RCT [19] compared a chemical

peeling agent (GA) to placebo for acne vulgaris. However, more than 10 chemical peeling agents have actually been applied. Further well-designed RCTs are needed to compare other chemical peels to placebo. A network meta-analysis based on these RCTs should provide more valuable and robust evidence for clinical practice. Additionally, the outcome measurements were significantly different across the included RCTs, which made it difficult to compare or merge the results of different studies. Therefore, we suggest that the future version of the guideline of care for the management of acne vulgaris should make recommendations regarding the standard of outcome measurements. Our review has some limitations. First, all included studies were of very low-to-moderate methodological quality with small sample sizes, which might have introduced bias. However, we evaluated for bias in each study. For example, most of the included RCTs did not describe the method of randomization. It is important to adhere to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement to avoid incomplete and inadequate reporting and to improve the quality of the evidence.[28] Second, this review did not investigate the effects of chemical peeling for acne scarring, although chemical peels are used clinically for this indication.[6] Finally, as previously discussed, the absence of a standardized peeling regimen limits the translation of our findings to clinical practice.

CONCLUSIONS

Implication for practice

Commonly used chemical peels appear to be similarly effective for mild-to-moderate

acne vulgaris and well-tolerated. However, based on current limited evidence, we could not draw a robust conclusion regarding any definitive superiority or equality among the currently used agents for chemical peeling.

Implications for research

Well-designed and well-reported RCTs are needed to provide high quality evidence to inform practice, particularly regarding the optimal formulation and regimen for chemical peeling agents. Comparisons with placebo or each other should be performed for various ethnic populations and skin types. In addition, standard outcome measurements for the management of acne vulgaris are needed.

ACKNOWLEDGEMENT

None.

COMPETING INTERESTS

All authors have not conflict of interest to declare.

CONTRIBUTORS

XC and LL designed the protocol. XC and MY searched the literature, extracted the data, and analysed the data. XC, SW, MY and LL interpreted the data and revised the manuscript.

FUNDING

This review was supported by a grant from the Sichuan Provincial Science and Technology Department (Grant number: 2017JY0277).

DISCLAIMER

The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report.

DATA SHARING STATEMENT

No additional data are available.

REFERENCES

1. Sathish D, Shayeda, Rao YM. Acne and its treatment options: a review. *Curr Drug Deliv* 2011;8(6):634-9.
2. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013;168(3):474-85. doi: 10.1111/bjd.12149
3. Kontochristopoulos G, Platsidaki E. Chemical peels in active acne and acne scars. *Clinics in Dermatology* 2017;35(2):179-82.
4. Salam A, Dadzie OE, Galadari H. Chemical peeling in ethnic skin: an update. *British Journal of Dermatology* 2013;169 Suppl 3:82-90.
5. Jackson A. Chemical peels. *Facial Plast Surg* 2014;30(1):26-34. doi: 10.1055/s-0033-1364220

6. Abdel Hay R, Shalaby K, Zaher H, et al. Interventions for acne scars. *Cochrane Database of Systematic Reviews* 2016;4:CD011946.

7. Arif T. Salicylic acid as a peeling agent: a comprehensive review. *Clinical, Cosmetic and Investigational Dermatology CCID* 2015;8:455-61.

8. Dreno B, Fischer TC, Perosino E, et al. Expert opinion: efficacy of superficial chemical peels in active acne management--what can we learn from the literature today? Evidence-based recommendations. *Journal of the European Academy of Dermatology & Venereology* 2011;25(6):695-704.

9. Sharad J. Glycolic acid peel therapy - a current review. *Clinical, Cosmetic and Investigational Dermatology CCID* 2013;6:281-8.

10. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74(5):945-73 e33. doi: 10.1016/j.jaad.2015.12.037

11. Ilknur T, Demirtasoglu M, Bicak MU, et al. Glycolic acid peels versus amino fruit acid peels for acne. *Journal of Cosmetic & Laser Therapy* 2010;12(5):242-5.

12. Levesque A, Hamzavi I, Seite S, et al. Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. *Journal of Cosmetic Dermatology* 2011;10(3):174-8.

13. Abdel Meguid AM, Elaziz Ahmed Attallah DA, Omar H. Trichloroacetic Acid

Vs. Salicylic Acid in the Treatment of Acne Vulgaris in Dark-Skinned Patients. *Dermatologic Surgery* 2015;41(12):1398-404.

14. Alba MN, Gerenutti M, Yoshida VM, et al. Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne vulgaris in teenagers. *Journal of Cosmetic & Laser Therapy* 2017;19(1):49-53.
15. Bae BG, Park CO, Shin H, et al. Salicylic acid peels versus Jessner's solution for acne vulgaris: a comparative study. *Dermatologic Surgery* 2013;39(2):248-53.
16. Dayal S, Amrani A, Sahu P, et al. Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. *J Cosmet Dermatol* 2017;16(1):43-51. doi: 10.1111/jocd.12266
17. ElRefaei AM, Abdel Salam HA, Sorour NE. Salicylic-mandelic acid versus glycolic acid peels in Egyptian patients with acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society* 2015;12(3):196-202.
18. Jaffary F FGSSHSM. Comparison the effectiveness of pyruvic acid 50% and salicylic acid 30% in the treatment of acne. *Journal of research in medical sciences* 2016;21(2)
19. Kaminaka C, Uede M, Matsunaka H, et al. Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study.

Dermatologic Surgery 2014;40(3):314-22.

20. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535. doi: 10.1136/bmj.b2535

21. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011 [Available from: www.handbook.cochrane.org.

22. Kessler E, Flanagan K, Chia C, et al. Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. *Dermatologic Surgery* 2008;34(1):45-50; discussion 51.

23. Kim SW, Moon SE, Kim JA, et al. Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. *Dermatologic Surgery* 1999;25(4):270-3.

24. Leheta TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. *Journal of Cosmetic & Laser Therapy* 2009;11(2):118-24.

25. Wahab IA, Pratt NL, Kalisch LM, et al. The detection of adverse events in randomized clinical trials: can we really say new medicines are safe? *Current drug safety* 2013;8(2):104-13. [published Online First: 2013/05/30]

26. Been MJ, Mangat DS. Laser and face peel procedures in non-Caucasians. *Facial Plastic Surgery Clinics of North America* 2014;22(3):447-52.

27. Handog EB, Datuin MS, Singzon IA. Chemical peels for acne and acne scars in asians: evidence based review. *Journal of Cutaneous & Aestheic Surgery* 2012;5(4):239-46.

28. Boutron I, Altman DG, Moher D, et al. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med* 2017;167(1):40-47. doi: 10.7326/M17-0046

FIGURE LEGEND

Figure 1. Preferred Reporting Items for the Systematic Reviews (PRISMA) diagram of the study flow.

Figure 2. Risk of bias summary for each study.

Figure 3. Risk of bias summary graph for all included studies.

SUPPLEMENTARY FILES

Supplementary Table 1. The search strategies for MEDLINE, EMBASE and CENTRAL via OvidSP.

Supplementary Table 2. Reasons for study exclusion

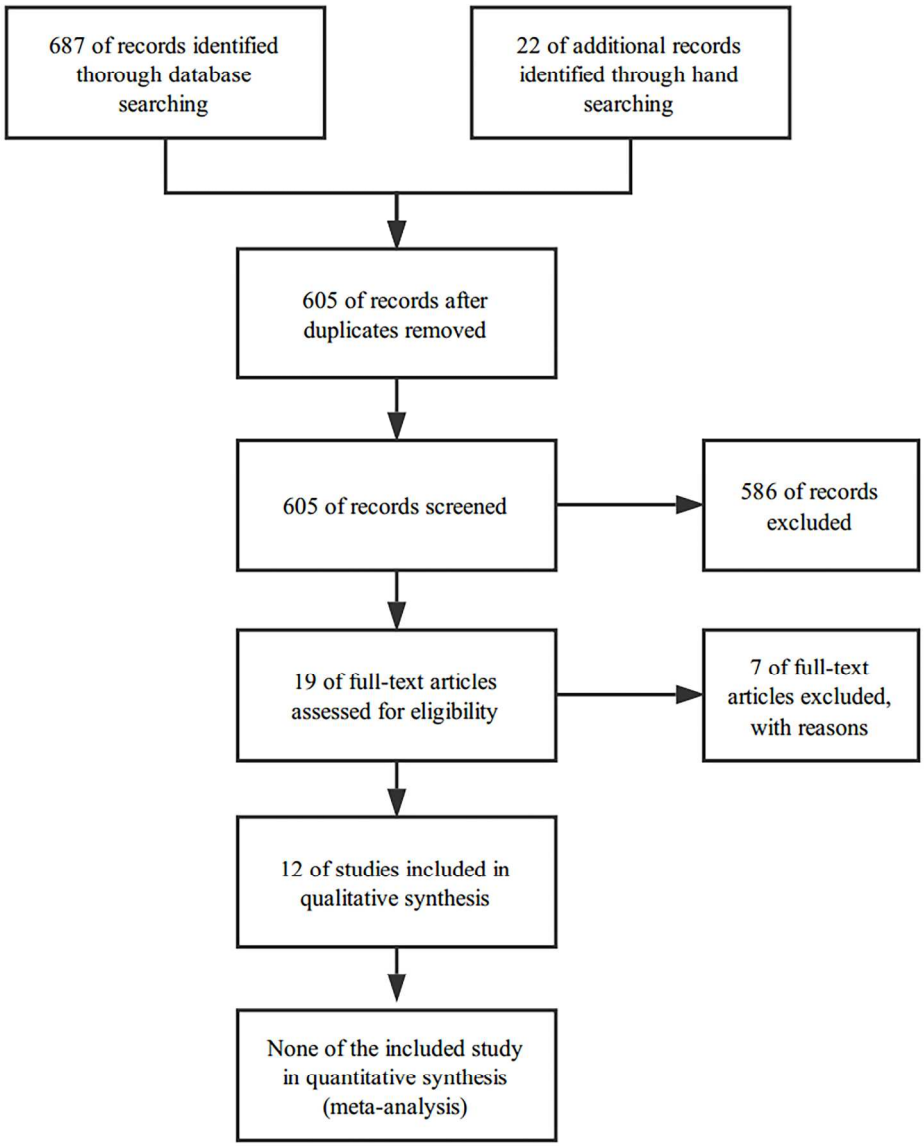

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) diagram of the study flow.

213x260mm (300 x 300 DPI)

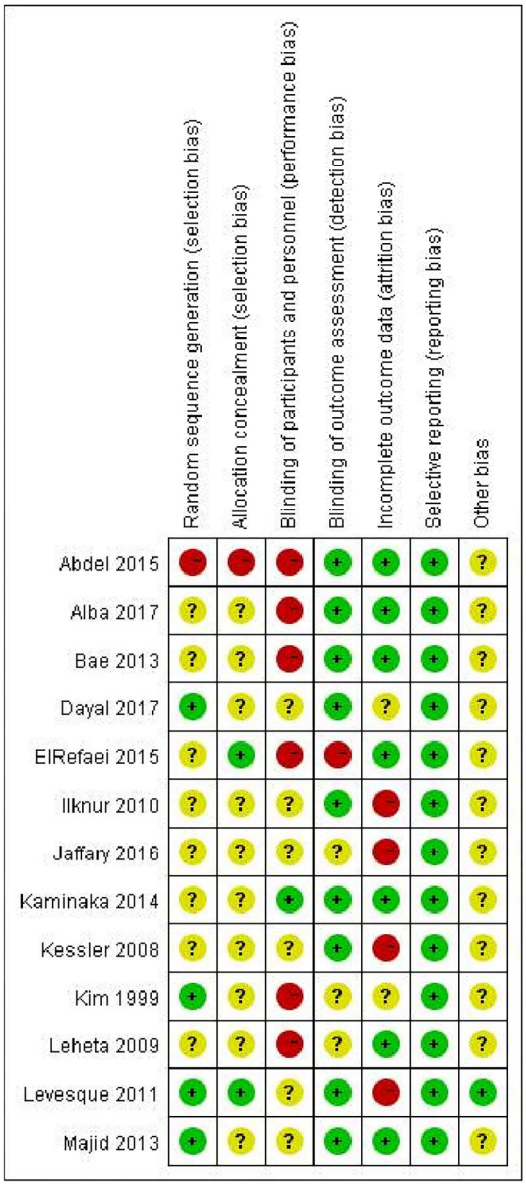

Figure 2. Risk of bias summary for each study.

138x297mm (300 x 300 DPI)

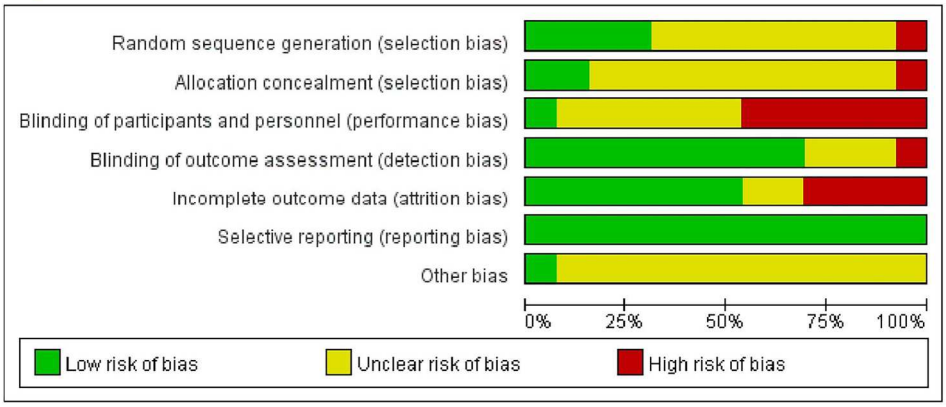

Figure 3. Risk of bias summary graph of all included studies.

209x87mm (300 x 300 DPI)

Supplementary Table 1. Search strategies for searching MEDLINE, EMBASE, and CENTRAL via OvidSP

No.	Searches
1	(chemical adj (peel* or resurface*).ab,kw,ti.
2	((hydroxy or glycolic or lactic or malic or citric or tartaric or salicylic or trichloroacetic or pyruvic or lipohydroxy or salicylic-mandelic or "amino fruit") adj acid*).ab,kw,ti.
3	("Jessner's solution" or "Jessner's solutions").ab,kw,ti.
4	(resorcinol* or phenol*).ab,kw,ti.
5	acne.ab,kw,ti.
6	exp *Acne Vulgaris/
7	1 or 2 or 3 or 4
8	5 or 6
9	7 and 8
10	remove duplicates from 9

Supplementary Table 2. Reasons for study exclusion

Studies	Reason for exclusion
Garg 2009 [1]	This study is not an RCT.
Kim 2015 [2]	This RCT compared alpha hydroxy acids plus an additional physical treatment with alpha hydroxy acids alone.
Lee 2006 [3]	This study is not an RCT.
Lekakh 2015 [4]	This study compared chemical peel and the combination of laser and chemical peel.
Nofal 2014 [5]	This study appears to be not an RCT because of the significant difference between the method section and the abstract about the randomization. And there is no reply from the authors to clarify this inconsistency.
Sharad 2011 [6]	This study is not an RCT
Wang 1997 [7]	This study is not an RCT

RCT: randomized controlled trial.

References of the excluded studies:

1. Garg VK, Sinha S , Sarkar R. Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: a comparative study. Dermatologic Surgery 2009;35:59-65.

2. Kim SJ, Baek JH, Koh JS, Bae MI, Lee SJ , Shin MK. The effect of physically applied

alpha hydroxyl acids on the skin pore and comedone. International Journal of Cosmetic Science 2015;37:519-25.

3. Lee SH, Huh CH, Park KC , Youn SW. Effects of repetitive superficial chemical peels on facial sebum secretion in acne patients. Journal of the European Academy of Dermatology & Venereology 2006;20:964-8.

4. Lekakh O, Mahoney AM, Novice K, Kamalpour J, Sadeghian A, Mondo D et al. Treatment of Acne Vulgaris With Salicylic Acid Chemical Peel and Pulsed Dye Laser: A Split Face, Rater-Blinded, Randomized Controlled Trial. Journal of Lasers in Medical Sciences 2015;6:167-70.

5. Nofal E, Helmy A, Nofal A, Alakad R , Nasr M. Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: a comparative study. Dermatologic Surgery 2014;40:864-73.

6. Sharad J. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. Journal of Cosmetic Dermatology 2011;10:317-23.

7. Wang CM, Huang CL, Hu CT , Chan HL. The effect of glycolic acid on the treatment of acne in Asian skin. Dermatologic Surgery 1997;23:23-9.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not necessary

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not necessary
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Meta-analysis is not possible to be performed.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not necessary
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Page 2 of 2