

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chemical peels for acne vulgaris: a systematic review of randomized controlled trials
AUTHORS	Chen, Xiaomei; Wang, Sheng; Yang, Ming; Li, Li

VERSION 1 – REVIEW

REVIEWER	Teruki Dainichi Department of Dermatology Kyoto University Graduate School of Medicine Japan
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	<ol style="list-style-type: none">1. Introduction is too long.2. In page 5, which studies was the recommendation of the previous guidelines (reference #7) based on? Please specify the references in the text.3. Concentration of each agents should be appeared in Table 1.4. Preparation for SA agents (in ethanol or polyethylene glycol) should be specified in Table 2.
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REVIEWER	Yoon Bum Kim Kyung Hee University, Seoul Korea
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	Content of this paper has already been reported publicly, There is no new information.
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REVIEWER	Elizabeth D Pienaar Cochrane South Africa, South African Medical Research Council. South Africa
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	<ol style="list-style-type: none">1. In the Methods section you state that you have used Standard Cochrane methodological procedures, however you search strategy does not include the standard Cochrane terms to accurately identify RCTs.2. Did you search Prospective clinical trial registries to identify any ongoing trials in the field?
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	<p>3. Risk of Bias of studies: for Random sequence generation, Allocation concealment and Blinding of participants and personnel there is a high percentage of uncertainty which means that the overall bias is higher for those studies. From figure two I would say that risk of bias is moderate and definitely not very low.</p> <p>4. In the description of the effects of the interventions I want to suggest that you add the reference to the specific trial at the first mention of the trial - this make it easier for the reader to see which trial you are describing.</p> <p>5. Suggest you add a subheading "Implications for Research" in the Discussion to clearly indicate where more research is needed. This will then be in line with Cochrane systematic review reporting.</p>
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REVIEWER	Kukuh Noertjojo Evidence-Based Practice Group, Clinical Services, WorkSafeBC. CANADA
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	<ul style="list-style-type: none"> - on page 6 line 11: Please explain what you mean by handsearched included AND EXCLUDED studies? You screened primary studies based on titles and abstracts only and there was no indication that you actually pulled the full paper to search the references on each of the excluded papers. - please explain how many studies identified from your search were in the form of review or systematic review or meta analysis on which you searched their respective references for relevant primary studies - grammar check please, e.g. page 6 line 42 (word "the" I think should be "be") - page 15 line 22: Comparison 5. Please provide reference. - page 21 line 11: I think you need to put registered trade mark symbol besides Vitalize peel and Micropeel Plus? - Figure 1. Please explain what you mean by other sources - Most of the primary studies compared active treatments and I think it makes it more difficult to really think of the effect of the treatment due to lack of placebo comparison. Can you discuss this issue further in your discussion. I notice there is one trial comparing it with placebo. - have you ever though of conducting network meta analysis given the available data?
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REVIEWER	Olalekan A. Uthman University of Warwick, UK
REVIEW RETURNED	18-Nov-2017

GENERAL COMMENTS	<p>Dear Editor,</p> <p>I was invited to review this manuscript with a particular emphasis on the statistical methods and analyses used. However, the authors stated that "Because of the significant clinical heterogeneity between the included RCTs, it was not possible to merge the data from different trials for meta-analysis."</p>
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REVIEWER	Oyelola Adegboye Qatar University, Doha
REVIEW RETURNED	20-Jan-2018

GENERAL COMMENTS	The manuscript by Chen et al., presents a systematic evaluation of the current evidence from randomized controlled trials (RCTs) regarding the effectiveness of chemical peeling agents for the
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	<p>treatment acne vulgaris. This is an interesting study. I have the following general comments:</p> <p>Page 7, lines 40-46; Could the authors elaborate on the term “clinical heterogeneity across studies” and why meta-analysis could not be carried out?</p> <p>Since the authors acknowledged the low methodological quality of the studies included in their manuscript, is their findings still valid? A sensitivity analysis would be helpful in this regard.</p>
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VERSION 1 – AUTHOR RESPONSE

The authors' responses are highlighted in yellow.

Editorial Requirements:

- Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study rather than summarizing the results.

Response: We added a Strengths and Limitations section to the abstract.

Comments from the Associate Editor:

This is a niche topic of most interest to dermatologists and doctors working in aesthetic medicine. I really liked Noertjojo's comments about the lack of placebo comparison in the studies and the suggestion that the next step should be a network meta-analysis (which would have been far more useful), which should be incorporated in the discussion. They should also mention whether this is the first systematic review on the topic, or discuss other similar studies, but I certainly didn't find another systematic review.

Response: Thank you. We agree with you on this point. To the best of our knowledge, this is the first systematic review of this topic. A network meta-analysis would certainly be more useful; however, we need additional RCTs to compare these chemical peels to placebo or other interventions using standard outcome measurements. We added this information to the Discussion section.

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Teruki Dainichi

Institution and Country: Department of Dermatology, Kyoto University Graduate School of Medicine, Japan

Please state any competing interests: none.

Please leave your comments for the authors below

1.

Introduction is too long.

Response: Thank you. In our opinion, a detailed introduction may be useful for the readers who are not familiar with chemical peeling, such as those who are not dermatologists. However, a few changes have been made to reduce the word count of this section.

2.

In page 5, which studies was the recommendation of the previous guidelines (reference #7) based on? Please specify the references in the text.

Response: We added these references to the text.

3.

Concentration of each agents should be appeared in Table 1.

Response: We did not add the concentration of each agent in Table 1 because the concentrations of these chemical peels used in different studies varied significantly. For example, the concentration of GA varied from 10% to 70% in different studies. More importantly, there is currently no consensus

regarding the optimal concentration or regimen of these chemical peels. Therefore, in our opinion, we should not add the concentrations of each agent to Table 1 to avoid misleading the readers.

4.

Preparation for SA agents (in ethanol or polyethylene glycol) should be specified in Table 2.

Response: We reviewed the full texts of all included RCTs; however, none reported the preparation for SA agents (in ethanol or polyethylene glycol). Therefore, we could not add the relevant information to Table 2.

Reviewer: 2

Reviewer Name: Yoon Bum Kim

Institution and Country: Kyung Hee University, Seoul Korea

Please state any competing interests: None declared

Please leave your comments for the authors below

Content of this paper has already been reported publicly, There is no new information.

Response: Thank you. However, we do not agree with this point. Although we could not perform a meta-analysis to combine the results of the included RCTs, we at least summarized the currently available evidence regarding chemical peels for acne. In fact, our review summarized 12 relevant RCTs. As we mentioned in the Introduction section, a recent guideline was only based on two RCTs and a previous guideline. In addition, our review highlighted the limitations of the current RCTs in this field. Therefore, our review provides valuable information regarding not only clinical practice but also future research in this field.

Reviewer: 3

Reviewer Name: Elizabeth D Pienaar

Institution and Country: Cochrane South Africa, South African Medical Research Council. South Africa

Please state any competing interests: None declared

Please leave your comments for the authors below

1. In the Methods section you state that you have used Standard Cochrane methodological procedures, however your search strategy does not include the standard Cochrane terms to accurately identify RCTs.

Response: The Cochrane search filters for identifying RCTs are designed to improve the efficiency of identifying eligible studies. Because only 687 records were identified through the initial database search, we decided to screen the titles and abstracts manually (instead of using the search filter recommended by the Cochrane group) to identify RCTs.

2. Did you search Prospective clinical trial registries to identify any ongoing trials in the field?

Response: We understand that the Cochrane Collaboration recommends searching clinical trial registries. Just as the Cochrane Handbook states, "It is also important to identify ongoing studies, so that when a review is later updated these can be assessed for possible inclusion. ... Awareness of the existence of a possibly relevant ongoing study might also affect decisions with respect to when to update a specific review." (Chapter 6.2.3). Because our review is not a Cochrane review and because there is no need to update it regularly, we did not search the clinical trial registries.

3. Risk of Bias of studies: for Random sequence generation, Allocation concealment and Blinding of participants and personnel there is a high percentage of uncertainty which means that the overall bias is higher for those studies. From figure two I would say that risk of bias is moderate and definitely not very low.

Response: We did not state that the risk of bias is very low. We stated that "The methodological quality of the included RCTs was generally low to moderate; however, in some cases, it was very low." (This means a moderate to high risk of bias).

4. In the description of the effects of the interventions I want to suggest that you add the reference to the specific trial at the first mention of the trial - this make it easier for the reader to see which trial you are describing.

Response: Most of the references in the Results section were listed in order of use. However, several references were also cited in the Introduction section; therefore, not all references in the Results section are in order of use.

5. Suggest you add a subheading "Implications for Research" in the Discussion to clearly indicate where more research is needed. This will then be in line with Cochrane systematic review reporting.

Response: In a typical Cochrane systematic review, the Conclusion section is divided into two parts: "Implications for practice" and "Implications for research." We revised our review according to your comments.

Reviewer: 4

Reviewer Name: Olalekan A. Uthman

Institution and Country: University of Warwick, UK

Please state any competing interests: None declared

Please leave your comments for the authors below

- on page 6 line 11: Please explain what you mean by handsearched included AND EXCLUDED studies? You screened primary studies based on titles and abstracts only and there was no indication that you actually pulled the full paper to search the references on each of the excluded papers.

Response: We followed the standard procedure for a systematic review. There are two steps for screening eligible RCTs. First, we screened the titles and abstracts to identify the article that might be an eligible RCT. We put these possibly eligible RCTs into a group (called GROUP A here). Second, we downloaded the full texts of all articles in GROUP A. Finally, we decided which ones would be included according to the information in the full text. The articles that were in GROUP A but we excluded during the second step were the so-called "excluded studies". The reasons for excluding these studies are listed in Supplementary Table 2. We handsearched the references provided in these "excluded studies".

- please explain how many studies identified from your search were in the form of review or systematic review or meta analysis on which you searched their respective references for relevant primary studies

Response: We hand-searched all bibliographies of the included and excluded studies and previous systematic reviews to identify further relevant trials. However, this step did not lead to any additional RCTs being used for our review. In other words, all relevant RCTs that were included previous in systematic reviews were also identified through our database search.

- grammar check please, e.g. page 6 line 42 (word "the" I think should be "be")

Response: Thank you. We corrected this error.

- page 15 line 22: Comparison 5. Please provide reference.

Response: Thank you. We added the reference.

- page 21 line 11: I think you need to put registered trade mark symbol besides Vitalize peel and Micropeel Plus?

Response: Thank you. We added the symbols.

- Figure 1. Please explain what you mean by other sources

Response: Other sources refer to the results of hand-searching. We revised this figure to make it clear.

- Most of the primary studies compared active treatments and I think it makes it more difficult to really think of the effect of the treatment due to lack of placebo comparison. Can you discuss this issue further in your discussion. I notice there is one trial comparing it with placebo.

Response: Yes, we agree with you. We added this point to the Discussion section.

- have you ever thought of conducting network meta analysis given the available data?

Response: Yes, we tried to perform a network meta-analysis, but we failed. The main reason for failure was the significantly clinical heterogeneity across the included studies. The participants, interventions (the type, concentration and regimen of chemical peeling agents), and outcome measurements were all significantly different across the included RCTs.

Reviewer: 5

Reviewer Name: Olalekan A. Uthman
 Institution and Country: University of Warwick, UK
 Please state any competing interests: None declared
 Please leave your comments for the authors below

Dear Editor,

I was invited to review this manuscript with a particular emphasis on the statistical methods and analyses used. However, the authors stated that "Because of the significant clinical heterogeneity between the included RCTs, it was not possible to merge the data from different trials for meta-analysis."

Response: Thank you.

Reviewer: 6

Reviewer Name: Oyelola Adegboye
 Institution and Country: Qatar University, Doha
 Please state any competing interests: None declared
 Please leave your comments for the authors below

The manuscript by Chen et al., presents a systematic evaluation of the current evidence from randomized controlled trials (RCTs) regarding the effectiveness of chemical peeling agents for the treatment acne vulgaris.

This is an interesting study. I have the following general comments:

Page 7, lines 40-46;

Could the authors elaborate on the term "clinical heterogeneity across studies" and why meta-analysis could not be carried out?

Response: We rewrote this paragraph to make it clear. We could not merge the results of two studies with significant clinical heterogeneity (just like we could not merge an apple with an orange). This is a basic principle of meta-analyses.

Since the authors acknowledged the low methodological quality of the studies included in their manuscript, is their findings still valid? A sensitivity analysis would be helpful in this regard.

Response: Yes, the low methodological quality may introduce bias into the results of these RCTs.

However, we did not perform any meta-analyses. We only summarized and described the results of the included RCTs. Therefore, a sensitivity analysis was not necessary.

VERSION 2 – REVIEW

REVIEWER	Teruki Dainichi Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan
REVIEW RETURNED	19-Feb-2018

GENERAL COMMENTS	<p>1 Based on the references, the authors must provide the precise information, such as concentration, and their vehicles, in some agents in Tables 1 and 2. The goal of the treatment with 30% GA and that with 70% GA; or that with 20% TCA and 35%< would be different. Clinical response of 30% SA in PEG and that in ethanol would be different particularly in Asian patients.</p> <p>2 In the abstract, the conclusion should be described more faithfully and modestly, and the study limitations should also be appeared in the abstract. It would not be appropriate to state that "Commonly used chemical peels have similar effectiveness for mild to moderate acne vulgaris" because of the very diverse designs of the existing studies, which are not yet sufficient for the present approach. The</p>
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	present study did not find any definitive superiority or equality of the current methods for chemical peels. This reviewer concerns this statement might not match to the clinical experiences of all the readership as for the safety and effectiveness.
REVIEWER	Kukuh Noertjojo Evidence-Based Practice Group, Clinical Services, WorkSafeBC. CANADA
REVIEW RETURNED	20-Feb-2018
GENERAL COMMENTS	Please check spelling again! for e.g. p. 4 line 14 - sbsequent. It should be subsequent. Please provide reference to Table 1. On p. 6 line 16 - excluded studies. Please explain this clearly? was it from 19 studies or from 586 studies (from line 21 page 8)
REVIEWER	Elizabeth D Pienaar Cochrane South Africa, South African Medical Research Council
REVIEW RETURNED	21-Feb-2018
GENERAL COMMENTS	All recommendations have been responded to by the authors

VERSION 2 – AUTHOR RESPONSE

The authors' responses are highlighted in yellow.

Editorial Requirements:

- Please provide more detail in the abstract, as per the requirements of the PRISMA checklist. For example, the abstract should include some numerical results.

Response: We revised the abstract according to your comments.

- Please remove the Article summary, as this is not part of journal format.

Response: Done.

- Please ensure the Strengths and Limitations section (after the abstract) is presented as a list of bullet points.

Response: Done.

- Please work to improve the quality of English throughout the manuscript, either with the help of a native speaking colleague or with the assistance of a professional copyediting agency.

Response: We revised our manuscript with the help of an English-language editing service.

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Teruki Dainichi

Institution and Country: Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Please state any competing interests: None

Please leave your comments for the authors below

1

Based on the references, the authors must provide the precise information, such as concentration, and their vehicles, in some agents in Tables 1 and 2. The goal of the treatment with 30% GA and that with 70% GA; or that with 20% TCA and 35%< would be different. Clinical response of 30% SA in PEG and that in ethanol would be different particularly in Asian patients.

Response: The purpose of Table 1 is to provide the abbreviations of the commonly used chemical peels for acne. As we stated in the 1st round of our responses to the reviewers' comments, the concentration of chemical peels varied significantly across studies (e.g., the concentration of GA varied from 10% to 70% in our included RCTs). Therefore, in our opinion, we should not add

concentrations to Table 1 to avoid misleading our readers. We revised the legend of Table 1 to make our purpose clear. However, we did present the concentration of each chemical peel in Table 2. Regarding the vehicles of these chemical peels, we carefully reviewed all included RCTs again. We included the information on the vehicles if the original RCT provided relevant information in their full text. However, the following studies did not provide the information about the vehicles of the chemical peels. Here, we have provided the screen shots of the Methods section of the studies.

- (1) Bae et al.
- (2) Dayal et al.
- (3) Ilknur et al.
- (4) Keseller et al
- (5) Leheta et al.
- (6) Levesque et al.

2

In the abstract, the conclusion should be described more faithfully and modestly, and the study limitations should also be appeared in the abstract. It would not be appropriate to state that "Commonly used chemical peels have similar effectiveness for mild to moderate acne vulgaris" because of the very diverse designs of the existing studies, which are not yet sufficient for the present approach. The present study did not find any definitive superiority or equality of the current methods for chemical peels. This reviewer concerns this statement might not match to the clinical experiences of all the readership as for the safety and effectiveness.

Response: We revised the conclusion in the abstract and in the full text according to your suggestion. Thank you.

Reviewer: 4

Reviewer Name: Kukuh Noertjojo

Institution and Country: Evidence-Based Practice Group, Clinical Services, WorkSafeBC. CANADA

Please state any competing interests: None declared

Please leave your comments for the authors below

Please check spelling again! for e.g. p. 4 line 14 - sbsequent. It should be subsequent.

Response: We have revised the typo and checked for spelling errors throughout the manuscript.

Please provide reference to Table 1.

Response: Done.

On p. 6 line 16 - excluded studies. Please explain this clearly? was it from 19 studies or from 586 studies (from line 21 page 8)

Response: The excluded studies were from the 19 studies. We added some information in the sentence to make this clear.

Reviewer: 3

Reviewer Name: Elizabeth D Pienaar

Institution and Country: Cochrane South Africa, South African Medical Research Council

Please state any competing interests: None declared

Please leave your comments for the authors below

All recommendations have been responded to by the authors

Response: Thank you.

VERSION 3 – REVIEW

REVIEWER	Kukuh Noertjojo Evidence-Based Practice Group, Clinical Services, WorkSafeBC
REVIEW RETURNED	14-Mar-2018

GENERAL COMMENTS	The authors have sufficiently address the suggestions/concerns given the reviewers. I very much appreciate the writing revision that makes it easier (and enjoyable) to read. I think this paper is ready to be published. Congratulations to the authors.
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REVIEWER	Teruki Dainichi Kyoto University Graduate School of Medicine Kyoto, Japan
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	The paper has been revised appropriately.
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