

Peer-Review comments and authors responses

Reviewer 1:

Comments:

1.TITLE: *To enhance the impact of your title and better reflect the focus of your mini-review, I suggest emphasizing the context of surgical wounds. For example, a title like "The Role of Vitamin C in the Healing of Tissue Wounds after Surgery: A Systematic Review of Randomized Controlled Trials" could highlight the specific context, making it more engaging for readers. Think about it.*

Response: We appreciate your feedback on our manuscript. We have discussed your recommendations and addressed your concerns. "The Role of Vitamin C in the Healing of Tissue Wounds after Surgery: A Systematic Review of Randomized Controlled Trials." After careful consideration, we changed it to: "The effect of vitamin C supplementation in wound healing: a systematic review of randomized controlled trials."

When we conducted our search, our population was not restricted to surgery, meaning that the terms "surgery" or "surgical" were not included, as we wanted to broaden our results. We are concerned that including "after surgery" might be misinterpreted as patients undergoing surgical procedures exclusively. Do you still think we need to include "surgical wounds"?

2. ABSTRACT:

a) Comment: *In the Background, you emphasize the significance of collagen in the process of wound healing. I suggest including a concise statement indicating that collagen type III is notably prevalent during this phase. It would be advantageous to incorporate this in the introduction section as well. Here is a potentially useful article: Singh, D., Rai, V., and Agrawal, DK. (Year). "Regulation of Collagen I and Collagen III in Tissue Injury and Regeneration." The citation is from the journal "Cardiology and Cardiovascular Medicine" published in 2023. The article is in volume 7, issue 1, and the page range is from 5 to 16. The document identifier for this publication is DOI: 10.26502/fccm.92920302.*

Response: Thank you for your valuable feedback regarding the significance of collagen in wound healing. We appreciate your suggestion to include a statement about the prevalence of collagen type III during this phase. We have revised the introduction to incorporate this information, highlighting its role in healing.

Additionally, We have referenced the article you provided (Singh, D, Rai, V, and Agrawal, DK. "Regulation of Collagen I and Collagen III in Tissue Injury and Regeneration." Cardiology and Cardiovascular Medicine, 2023, Volume 7, Issue 1, Pages 5-16, DOI: 10.26502/fccm. 92920302) to support this discussion.

b) Comment: *In the outcomes, when discussing the influence of Vitamin C on ulcers, kindly clarify the specific type of ulcers (such as skin ulcers or pressure sores) to prevent any mistake with corneal ulcers. Incorporating the clarification from the extended results section into the abstract would improve reader understanding.*

Response: Thank you for your constructive feedback regarding the discussion on the influence of Vitamin C on ulcers. We appreciate your suggestion to clarify the specific types of ulcers mentioned in the manuscript. We have revised the text to specify that we focus on skin ulcers and pressure sores, ensuring no confusion with corneal ulcers. Moreover, we have incorporated relevant clarifications from the extended results section into the abstract to enhance the reader's understanding.

c) Comment: *About safety considerations, you mentioned safety concerns in your cover letter, but the manuscript itself does not provide much data on this topic. If safety was a significant aspect of your research question, I recommend making this more visible, perhaps by expanding on it in the discussion section.*

Response: The articles included in this review did not assess the safety of Vitamin C, which we stated as a safe intervention.

3. CONCLUSION

a) Comment: *I have one final question regarding your conclusion. Does the improvement in wound healing after surgery also correlate with a reduced risk of infection? If so, you might consider including this point in your rationale to further strengthen your argument. Overall, your work is impressive, and I appreciate the opportunity to review it.*

Response: The rate of infections was vaguely mentioned in only one of the articles (Farahani-Jam et al, 2022), being lower in the Vitamin C group, therefore, we considered that it was not appropriate to include in our conclusions, as the authors didn't share the details. We also made the decision to add only outcomes related to wound healing.

Reviewer 2:

TITLE:

a) Comment: *Once the review included trials with vitamin C supplementation and the goal is to assess the role of this supplementation in wound healing, I would consider changing the title to: "The role of vitamin C supplementation in wound healing: a systematic review of randomized controlled trials".*

Response: Thank you for your kind words. We evaluated your recommendations and made the appropriate changes. After careful consideration, we changed it to: "The effect of vitamin C supplementation in wound healing: a systematic review of randomized controlled trials." We understand the importance of this specific detail, stating "supplementation" to avoid confusion from dietary food intake of Vitamin C.

AUTHORS SECTION:

a)Comment: *In the authorship section, there is an indicator "b" that has no legend or person assigned to it. Emails should be reported in lowercase letters.*

Response: Authors' affiliations were properly disclosed and corrected the email recommendation.

Abstract and Methods:

a)Comment: *The term "soft tissue wound healing" is controversial in this situation, as in some*

cases the wound includes skin or mucosa. My suggestion is to include "skin and soft tissue," or remove "soft tissue" and use "wound healing" only. "The research question and eligibility criteria were defined using the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework." – I suggest that if the use of PICOS and the research question is mentioned, you should include the results of them in the methodology. I suggest changing the name CENTRAL to Cochrane Central Register or Cochrane.

Response: We appreciate your feedback. We have corrected the term to “skin and soft tissue” on both sections. Additionally, we disclosed our research question and PICOS in detail, and changed the term “CENTRAL” to “Cochrane Central Register of Controlled Trials (CENTRAL)” to avoid confusion, as well as the typographical errors.

DISCUSSION:

a)Comment: *The first discussion paragraph has many words in parentheses which significantly hinders readability. In my view, it would be beneficial to reduce the number of words in the discussion, as there are situations that are repeated several times in the article, such as the heterogeneity between procedures. I recommend discussing heterogeneity only once and how it affects the understanding and interpretation of the article.*

Response: Thank you for your valuable feedback regarding the discussion section. We appreciate your point about the excessive use of parentheses, and we worked to streamline the text for better readability. We also acknowledge your suggestion to reduce repetition, particularly concerning the heterogeneity between procedures. We consolidated the discussion of heterogeneity into a single, focused section that clearly outlines its impact on the study’s findings. Your insight helped us to enhance the clarity and the effectiveness of the discussion.

CONCLUSION:

a)Comment: *I recommend making the conclusion section more assertive about what you studied and under what conditions. Here, subgroup analysis can help clarify the data. Additionally, discuss how vitamin C supplementation could be studied and help address the remaining open questions, citing them (e.g., randomized clinical trial with pre-specified types of surgery, standard doses of vitamin C, and a control group comparable to the intervention).*

Response: We addressed your concerns and made the necessary changes.

Reviewer 3:

a)Comment: *Congratulations on your mini-review regarding the effect of vitamin C on wound healing. Your introduction effectively sets the stage for the topic, your methods clearly outline your workflow, and your results are well presented. In the discussion, you successfully explain your findings and acknowledge the limitations of the study. While your findings are limited by the heterogeneity and small number of studies, your work is particularly valuable in highlighting the lack of reliable studies on this topic. I was surprised to find so few RCTs evaluating the effect of ascorbic acid on wound healing, this gap represents a relevant, feasible, and intriguing area for future research. Despite the challenges, you have done an excellent job of identifying and discussing these limitations and the possible conclusions within the available data.*

Response: Thank you for your thoughtful and encouraging feedback on our mini-review. We're grateful for your recognition of our efforts to highlight the current limitations in studies on Vitamin C and wound healing, especially the surprising scarcity of rigorous RCTs on this topic. Thank you again for your kind words and valuable insights.

Reviewer 4:

INTRODUCTION:

a)Comment: *The Introduction should be revised. Centering the introduction on vitamin C from the outset would create a more engaging narrative by directly aligning with the review's objectives. Instead of overwhelming the reader with the complexities of the entire wound healing process, the introduction should focus on how vitamin C affects key stages of healing, such as collagen synthesis, antioxidant activity, and immune modulation. Additionally, expanding on existing literature gaps would emphasize the novelty of the review, provide a strong rationale, and reinforce its clinical significance. Finally, the review question should be explicitly added to establish the aim of the mini systematic review.*

Response: We appreciate your feedback. We have included key points about Vitamin C as you suggested.

METHODS:

a)Comment: *The Methods section requires enhancements for clarity and conciseness. A more detailed description of the "Population" is necessary to provide a better context for the study. Additionally, the outcome measure and the "standard of care" should be clearly defined, as their variation across studies may impact comparability. The phrase "all the authors" requires clarification in study screening and data extraction. Using independent reviewers to assess citations for inclusion can help reduce the risk of random errors and bias. It would also be helpful to clarify the reasons for choosing the original RoB tool over the updated RoB 2 tool.*

Response: We appreciate your feedback and want to address your concerns: We apologize for any confusion caused by lack of definition of our PICOS reasoning, the details were included. We see that "standard of care" is not clearly defined. The two studies that did not use placebo don't mention exactly how the control group was treated, except for remarking that they did not receive vitamin C, as they were treated with the same procedures as the intervention group, we have changed "standard of care" for "usual care".

We have removed the inconsistencies and replaced them with a clearer explanation of how we perform data extraction. Also, the reason for choosing RoB over RoB2 is that RoB is integrated in the Covidence platform, which we used for independently assessing risk of bias. As the tools represent similar assessments, we have initially chosen to maintain the RoB tool.

RESULTS:

a)Comment: *The Results narrative requires minor style revision. I could not locate Table S1 in the supplementary material. In fact, it only contains the detailed search strategy. Furthermore, the*

flowchart highlights the reasons for excluding specific studies, which may be sufficient. The main findings should be reviewed to proper include not only the p-values, but the effect sizes and confidence intervals, where applicable, to further strengthen the presentation of the results. The "Table 1" layout needs to be adjusted to enhance the clarity and organization of the data.

Response: Thank you for all comments and suggestions made in order to make Table 1 more clear and organized. We kindly incorporated all of them and would like to make a few explanations about some of the comments.

b)Comment: *Kindly review the table layout to enhance the clarity and organization of the data*

Response: We reordered the articles according to the wound type/procedure and changed the order of two columns (Time point and duration of follow-up and Total sample size). Besides, some of the additional information requested were added as footnotes.

c)Comment: *Could you please clarify whether you are reporting in absolute numbers or percentages? Also, consider providing a brief legend or footnote explaining the abbreviations used.*

Response: For gender, all data were reported as percentages (an indication was added as footnotes). We updated the list of abbreviations used in the table. Thank you very much for checking and highlighting it.

d) Comment: *It is important to clearly define both the primary outcome and the outcome measure.*

Response: Unfortunately, not all studies provided a clear description about the outcome measure. For those who did, we added the information in Table 1 or as a footnote.

e) Comment: *Detailing the statistical analysis methods employed could provide deeper insights into the robustness of the findings. Including effect sizes and confidence intervals, where applicable, would further strengthen the presentation of results.*

Response: We totally agree that the information regarding effects sizes and confidence intervals would strengthen the presentation of the results and the robustness of the findings. However, none of the RCT included in our review provided such information, only the p-value. In fact, three studies (Boyd et al., Taylor et al., and Ramasubbu et al.) did not include a description of the statistical analysis in the Methods section.

f) Comment: *Please clarify whether you are presenting the data as mean and standard deviation, or as median and range. You should clarify the three group pairs used in this study. It would be nice to specify the type of placebo used to mask the intravenous administration of Vitamin C. Should it be normal saline?*

Response: The information was added as a footnote.

g)Comment: *You should clarify what is the standard of care in this study.*

Response: The “standard of care” is not clearly defined. The two studies that did not use placebo don’t mention exactly how the control group was treated, except for remarking that they did not receive vitamin C. As they were treated with the same procedures as the intervention group, we have changed “standard of care” for “usual care”.

h) Comment: *For N/A, please indicate if the variable was not reported in the main paper.*

Response: The abbreviation N/A was replaced by “not mentioned” in the table to make the information clear.

DISCUSSION:

a)Comment: *The discussion needs major style revision. There should be a focus only on the key findings from the review, and the clinical / research implications (to mention how the study's results might influence future research) and limitations. Comparisons with the literature should be more thoroughly addressed. A structured "discussion" model is presented, as follows: "This mini-review found that ... (add a summary of the important or interesting results). In turn, in agreement with other studies... Previous evidence has indicated an overall beneficial effect of To our knowledge, this is the first mini-review that assessed the (add other strengths). The present findings are clinically important, notably Some controversy exists on ... Further research is thus needed to determine.... Limitations must be acknowledged, particularly.... " I recommend considering the above suggestion and modify accordingly.*

Response: Thank you for your valuable comments on the discussion section of the mini-review. We appreciate your guidance on how to structure this part more effectively. We have revised the section to emphasize the essential findings and clearly outline our results' clinical and research implications. Incorporating your suggested framework, we have organized the discussion as follows:

- 1.- Summary of findings: We have included the essential results.
- 2.- Literature Comparisons: We expanded the comparison with existing literature to provide a more comprehensive context for our findings.
- 3.- Clinical importance: We highlight the clinical significance of our results.
- 4.- Controversies and future research.- We addressed existing controversies and suggested areas for further research.
- 5.- Limitation: We acknowledged the limitations of our study.

Thank you for your recommendation; we have greatly enhanced the clarity and impact of the discussion.

Reviewer 5:

a)Comment: *Great job everyone! This manuscript addresses an important topic in wound healing and its relationship with vitamin C. You all have conducted a thorough investigation using the correct methods for a systematic review. Overall, the study is well-conducted, but there are some areas that require small revisions. Again, good job!*

Response: Thank you very much for your valuable feedback and insightful comments on our manuscript. We appreciate your thoughtful evaluation and are grateful for the opportunity to improve our work based on your suggestions. We believe it has strengthened the overall quality of

our paper. The changes have been incorporated throughout the manuscript, and we're looking forward to hearing back from you.