Author’s response to reviews

Title: The use of urea for the treatment of onychomycosis: a systematic review

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Author’s response to reviews:

We would like to thank the reviewers for their constructive feedback. We have supplied a copy of the manuscript with modifications visible. We hope this is suitable for your reviewing requirements.

Please find our response to the reviewers below.

Reviewer #1:

1. Line 39: Would you have included broader laboratory tests such as PCR or PAS staining for diagnosis (if they had been uncovered) as they may have a higher diagnostic accuracy - currently the review only covers microscopy and culture which although are standard may not be gold standard.

Response: Reviewer 1 is correct, we did consider all objective diagnostic tools, however, we did not identify any studies that applied PCR or PAS staining. To better reflect this, amendments have been made in the abstract (line 39) and methods (line 161) to acknowledge all laboratory based diagnoses was acceptable. An example from line 161 is below:

“...or alternative laboratory-based tests (e.g. polymerase chain reaction (PCR) testing or periodic acid–Schiff (PAS) staining),...”

2. Line 119: Urea has keratolytic properties but I qualify this statement and suggest that it is at only at higher percentages (above 30%) as below these percentages it has humectant properties.

Response: A sentence has been added (and cited) to state “Urea, in concentrations over approximately 30%, is considered a keratolytic...[reference].” (line 119)
3. Line 136: Delete the word "including" as all 10 sources were listed.

Response: Actioned, thank you (line 136).

I note that Reviewer 1 has already accepted the manuscript and trust that the editorial team will find these modifications suitable and in keeping with Reviewer’s 1’s suggestions.

Reviewer #3:

1. In the ‘Studies included for the review’ section (lines 155-157), to include your reasons for incorporating a range of study designs. Randomised controlled trials are usually considered the 'Gold standard', however presumably here you are not expecting to find sufficient studies on this topic to limit the search to RCT's only. I would state this rationale, even if it appears obvious to the authors, as some systematic review assessment tools (e.g. AMSTAR-II checklist) have this as a quality check criteria.

Response: The rational for the broad range of included study designs was indeed due to our concern there would not be a sufficient number of studies on the topic. We have updated the manuscript to reflect this by beginning the section with the sentence “To maximise the potential for data capture…” (line 155). We hope you find this suitable.

2. Further to the above, you perform a quality assessment of your included studies using the McMaster critical appraisal tool. I would link your findings from this into your descriptive summary to make it clear to the readers, which likely will include clinicians and practitioners, which of your included outcomes are supported by the higher quality evidence. For example, I would emphasis in the text that both of your included RCT’s support the safety of urea for the treatment of onychomycosis with one further supporting its efficacy, especially given that you have very limited data on this outcome.

Response: Thank you for the suggestion. We have updated the Summary of cure results and the Safety of urea for the treatment of onychomycosis sections to emphasize the outcomes of the higher levels of evidence within the manuscript (Lines 313 – 314 and 321 - 324 respectively) as indicated below.

“Although a limited number of studies were identified, two [30, 31] presented results of RCT study design, representing the higher level of evidence. These RCT studies indicated effectiveness of urea when used with other medicaments for clinical improvement and mycological cure [30, 31] and complete cure [31] respectively.”

And

“Of these, three [30, 31, 35] studies reported mild to moderate adverse events including: periungual maceration in 25% of participants (3 of 12) of a comparative study [34]; redness and
tingling in less than 1% of participants (1 of 70) in an RCT study [30], and; in an alternative RCT [31], 94.1% of participants reported local tolerability (99 of 105) with urea treatment. This last RCT also reported 30% of participants were ‘very’ satisfied with the overall efficacy of urea treatment upon completion of the study [31].”

Thank you again for the suggestions and we hope this is to your satisfaction.