Author’s response to reviews

Title: The role of tonsillectomy in the Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis syndrome; a literature review

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Version: 4 Date: 28 Nov 2017

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Reviewer reports:

Anders Fasth (Reviewer 1): As previously I find this a sound study performed according the rules (PRISMA) for a systematic literature review and and I have no new comment on the method based on the comments given by the other two reviewer. Methods and Results do not need any further changes. Thus, the issue is whether or not any minor changes could improve the manuscript related to Introduction and Discussion.

In the Introduction you could add within parenthesis after short ("short () regularly episodes") a time frame = 3-5 days. Also a line on that the febrile episodes are accompanied by a marked inflammatory response with CRP > 100 mg/L with complete normalization between the episodes.

Response: We agree and have included these remarks (page 4, line 58 and line 60).

After reading the comments by reviewer 2, I think adding a little more on the clinical presentation is essential as obviously many ENT physicians have limited knowledge about PFAPA.

Response: This was performed in the second revision as stated, also the introduction has been extended regarding diagnostic criteria as suggested by reviewer 4 (page 4, line 66-73).

Reviewer 3 have given some suggestion for the Discussion and those have improved this part and thus I have no further comments.

Mustafa ÇELİK (Reviewer 3): Dear authors,

The paper is now excellent and more clearer.

I am happy to accept it.
Best wishes.

Michael Hofer (Reviewer 4): This is an interesting paper reviewing the evidences in favour of TE/ATE as treatment for PFAPA syndrome. The authors reviewed the literature and analysed the publications according to a quality score, proposed by them. Compared to the recent Cochrane analysis, the authors add a systematic review of all published case series.

It is still not clear for me what is the real added value of this article as compared to the Cochrane review. I understand that case series were added and that the number of patients is higher, but the quality of most of these studies is low. I am not convinced that adding low quality articles may improve the evidence, nor help the clinician in his therapeutic choice. In the results, I would show the results of the high quality studies separately. The authors should clearly discuss what is new in their article in terms of conclusion drawn by the data.

Response: As discussed in the paper, the effect of TE/ATE in PFAPA has been reported in only two RCTs but also several case series. Isolated, each case series has little impact, but as there are several case series we consider it of value to sum up what they have shown, which is the aim of this review. For clinicians searching for the evidence for TE in their patients, this review must be an easier and more efficient approach than reading several case series. This may especially be of interest as there are only two RCT, and as discussed, one of them with questionable quality.

We have extended the presentation of results regarding the rate of success of TE in case series with low/moderate and high quality (which are presented separately as suggested) (page 7 line 134 – page 8 line 138). We have extended the discussion to underline the conclusion drawn by the data (page 9, line 175 and further).

The authors wrote in the methods: "High quality study should have included patients according to definitions by Marshall or Thomas". In the Renko study, many patients did not fulfill the criteria. I would discuss this point and not only refer to both RCTs.

Response: We already had included in the first paragraph of the discussion that the study by Renko had vague diagnostic criteria and has been criticized for that, but has no also added that they were not according to Marshall or Thomas. As discussed, this limits the quality of this study.

Please explain the rational of limiting the high quality case series to both above definitions.

Response: There is no international consensus on the diagnostic criteria, but the criteria by Thomas or Marshall are the most widely used. By using these principally equivalent criteria, more homogeneous patients are included in different studies. Including patients with other diagnostic criteria increases the possibility that other patients than those with typical PFAPA are included, and consequently the generalizability from results in these patients would be reduced.
In the background, the problem with accurate PFAPA diagnosis should be discussed and what is the difference between Marshall and Thomas criteria.

Response: We have included this in the background in a rewritten and extended paragraph. We have also included a sentence in the discussion underlining the importance of clear and similar definitions between studies (page 8, line 151-152).

Retrospective diagnosis is compatible with high quality in the evaluation of article quality if both other conditions are present; I would not consider as high quality a study using retrospective diagnosis, in particular because I do not see how the removal of the tonsils would facilitate the diagnosis.

Response: We agree, and only studies with a prospective diagnosis according to Marshall or Thomas were included as high quality studies, i.e. all three criteria should be fulfilled to be a high quality study.

Another problem is the comparison between ATE and TE; this should be mentioned in the table. What was the rational of ATE in PFAPA patients?

Response: Information about the number of patients in each study also subject to ATE was included, but we have now added the % of total number in the table to increase the readability of this information.

The rationale for performing ATE is not given in studies; this has been performed on the discretion of the surgeons in each series. Therefore we also discuss that the impact of performing ATE and not only TE in patients with PFAPA is not known and should be studied further.