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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Author’s response to reviews:

Saeedia Khwaja (Reviewer 2):

I think in the UK, we have strict Scottish sinus guidelines on indications for tonsillectomy and hence I am not clear what criteria was used in these studies. Also there seems to be a mix of pt groups.

1. Well children with acute bacterial tonsillitis who will have fever, adenitis, pharyngitis

2. Unwell children who have viral tonsillitis leading to bac tonsillitis with the same symptoms above and immature immune systems.

Hence the diagnostic criteria is not robust enough to differentiate these 2 groups hence the variable results.

Reply: It seems for us that the reviewer has not seen that this manuscript is only dealing with children with the PFAPA syndrome. Criteria for tonsillectomy for other reasons then PFAPA are not relevant for this group. We have not discussed acute tonsillitis or recurrent bacterial tonsillitis, we include only children with PFAPA. We think we have thoroughly discussed the criteria for PFAPA in the different studies presented.

I am slightly confused by the message of the review. In essence this paper is agreeing with the cochrane reviews by adding in the case reports which are of variable quality. So what?

So what do I learn extra from this paper?

Reply: We have discussed this in the manuscript. In addition to the two RCT-studies and the Cochrane review there is a substantial number of case reports. These have not been summarized in a review before, and we think that adding this literature review of these studies add to the knowledge about the effect of tonsillectomy in children with PFAPA, especially since there are only two RCTs.
1. Surgery outweighs observation regardless of quality of the paper. Hence tonsillectomy benefits even if the pt has only one symptoms.

2. Stricter diagnostic criteria of the syndrome, brings in 2 issues, tonsillitis, and immature/weak immune system hence success of surgery decreases as it tackles only one component, so there is a mix of pts in the cohorts.

Reply: We do not understand what the reviewer means. The comment may be a consequence of that the reviewer has not understood the group of patients studied.

Can I suggest a relook at what new message is being delivered, rather than critiquing the cochrane review failings, but yet agreeing with its outcome. If u can suggest a theory and explanation of the data would be interesting. See above as an option.

Reply: As above, we think that this comment also is based on a misinterpretation of the patient group being studied.

As a consequence, no alterations has been made in the manuscript according to reviewer no 2.

Mustafa ÇELİK (Reviewer 3): The role of tonsillectomy in the Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis syndrome; a literature review.

The authors investigated the effect of the tonsillectomy or adenotonsillectomy on outcomes on children with PFAPA syndrome. Etiopathogenesis of PFAPA syndrome remains unclear and some theories have been recommended for the explanation of its pathogenesis. Although its pathogenesis remains sparse, curative treatment has been investigated in previous studies. Considering the literature knowledges, tonsillectomy or adenotonsillectomy improve the outcomes of these patients and other therapies has not enough adequate level of the evidence. I agree with the authors with respect to requirement of future randomized controlled studies. Considering current conditions, the present study is valuable study for researchers. Some recommendations need to improve the manuscript for publication;

I invite you to improve your manuscript due to my following questions;

**Background should be improved and specified about the lack of PFAPA treatment.

Reply: We have included a short paragraph stating that no other curative treatment options are available

**Methods should be more specified.

1. **When was the diagnosis of PFAPA set for children? Is it important condition for outcomes of tonsillectomy?
Reply: We have presented for each study if the diagnosis was set prospectively before surgery, or retrospectively after surgery. A more exact indication of the time or age of children are very inconsistently reported in the articles.

2-**What is the rates of spontaneous resolution of PFAPA according to current literature?**

Reply: It is beyond the aim of the manuscript to describe this, we aimed to give physicians the best basis for the decision to operate or not. However, the decision to perform tonsillectomy may also be based on the knowledge of the rate of spontaneous resolution. We have therefore included a paragraph about this at the end of the discussion.

**Discussion should be more specified and improved.**

3-** How should we decide the tonsillectomy for PFAPA?**

Reply: Our aim was to provide an as solid basis as possible for the physicians to decide upon tonsillectomy or not in children with PFAPA. However, this decision must also rest upon knowledge about the alternative, especially the rate of spontaneous resolution. As discussed above, we have therefore included a paragraph about this at the end of the discussion.

4-**What are the eligibility criteria for tonsillectomy in children with PFAPA syndromes?**

Reply: No such criteria have been postulated, and such criteria (as discussed above) must be based on more factors than discussed in this manuscript. We therefore do not consider it appropriate to suggest such criteria, which could rather be the task for an expert group to perform. However, a paragraph shortly discussing different treatment options has been included at the end of the discussion.

5-**What is your recommendation for researchers about PFAPA with respect to follow-up period of children?**

Reply: we also think that this is beyond the scope of this study.

6-**What is the clinical implication of the present study?**

Reply: The clinical implications is that these results adds to the knowledge the decision about tonsillectomy in children with PFAPA should be based upon. We think that this has been addressed in the additional paragraphs we have included and discussed above, and also extended the conclusion.