The Editor 2016-11-14

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Dear sir

Thank you very much for informing us about the outcome of the review process for our paper entitled: Impact of gastroesophageal reflux control through tailored proton pump inhibition therapy or fundoplication on Barrett's esophagus. We are deeply indebted to the careful review process which our manuscript has been subjected to and appreciate the very constructive criticism. We have commented upon each individual reviewers' point and have made appropriate changes in the revised manuscript which are highlighted in review mode in one of the enclosures.

Hereby we sincerely hope that the manuscript will be found suitable for publication in your distinguished journal.

Sincerely yours

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Comments on the reviewers' reports

Reviewer 1

First of all we thank this reviewer for his/her very helpful comments that we here address step-by-step.

Q: The surgery group has a more-than-expected percentage of pathologic reflux even though patients are asymptomatic. I cannot understand how this subgroup can contribute to the study. They are in fact just like non-operated patients at baseline.

A: It is true that some of the operated patients eventually presented with abnormal acid reflux variables, despite the fact that these patients were judged to be symptom-free at the time of the telephone interview. Indeed, this observation highlights two things. Some of the operated patients with long-segments BE might have significant remaining reflux despite being judged to be asymptomatic. We have put this into focus with one additional sentence in the discussion. Secondly, these data illustrate the well-known fact that antireflux surgery in long-segment BE patients might not be as successful as in chronic GERD. The great advantage of having the entire cohort of these patients included allowed us to make a comparison within the group between those with all reflux eliminated and those with remaining reflux of some magnitude. This is also pointed out in the discussion (page 11/12).

Q: Patients in group 2 with reflux and without reflux have significantly different GERD_HRQL scores. How?

A. Please see the above comments. It is well known that BE patients may be considered asymptomatic when questioned by use of superficial approaches, whereas when more dedicated instruments are used found to present distinct symptoms as picked up by the currently used instruments. Regarding the advantage of this final balance see also the above comments

Q. Patients with a successful fundoplication are GERD-free for at least 5 years. Is this comparable to a short-course PPI therapy? Do group 1 patients had PPI for the first time in their life or were taking the medication before? For how long?

A. All BE patients enrolled into the study had PPI for a long period before enrolment. We were unable to specify the number of years under which these patients had been treated before inclusion. We have added this information in the revised manuscript (page 4). We have also discussed the potential importance of the "wash-out period" as well as the 8 weeks of treatment by the individual doses of PPI. Again the relevance of the chosen time period is illustrated by the lack of difference in the studied outcome parameters between the BE patients being pH normalized on respective dose of PPI and those operated patients who were considered to be without any kind of reflux for at least 5 years.

All these aspects have been addressed in the revised manuscript.

Q. A significant % of patients in group 1 are "PPI resistant". Please inform which measures were taken to assess that patients were taking medication correctly, were not taking pantoprazole before and had tolerance to the medication, etc.

A. In our opinion only one of the BE patients enrolled was “PPI resistant” according to the generally accepted criteria (see Zerbib et al.). All but one of those who had shown partial response or intolerance to pantoprazole, responded to a switch to another PPI. We put a lot of emphasis on the compliance (controlled by interview and return of the remaining medication at each visit). None had a history of incomplete response to respective regimen before enrolment.

Q. The clinical significance of this study is, for me, that esophageal neutralization is hard to obtain in patients with PPI. However, the authors showed that does not really matter if GERD control is objectively achieved or not (I am not sure if a long-term follow-up would change this concept). A good contribution would be to identify predictors for not achieving GERD control. Some were analyzed but dispersed throughout the manuscript (age, BMI) while others were not analyzed (esophageal motility).

A. We do agree that current evidence speaks in favor of the continued surveillance of BE patients based on the concept of symptom control. We strongly believe that a focused study on predictors of failure requires substantially greater amounts of patients, why we have deliberately avoided going into the details of a similar analysis. This remains true not the least for the esophageal motility data.

We have addressed some of these issues in the discussion.

Q. Figure 2 should not have "survival" included

A. Corrected

Comments on the reviewers' reports

Reviewer 2

First of all we thank this reviewer for his/her very helpful comments that we here address step-by-step.

Q. The title is misleading. The study is of very short duration and is not designed to study any effect of PPIs or fundoplication on Barrett's esophagus.

A. We agree! Indeed, it should read **in patients with** Barrett's esophagus, but not **on** Barrett's esophagus. We have changed the title accordingly.

Q. In abstract, conclusions are wrong and not supported by the results. In PPI group, there was improvement in symptoms between untreated to PPI once daily group. But no further improvements are noted with escalation of the doses.

A. We partly agree and have made appropriate adjustments.

Q. The objectives are too many. The authors keep mentioning about acid reflux variables throughout the manuscript but the only value shown is the total acid reflux. Instead of using normal versus abnormal reflux, it is best to divide groups into normal pH study versus abnormal pH study.

A. We would like to thank reviewer for this comment. We used the most accepted definition for normal/abnormal acidic reflux (ref 15). As stated in results we also tested for supine or upright body positions reflux.

Q. Do authors have manometry findings in these patients?

A. We have not performed a detailed analysis of manometry measurements, except for the proper localization of the LES and positioning of the pH electrode for ambulatory monitoring, as this is outside the scope of this study.

Q. Under RESULTS section, subheadings such as Demographics, Normalization of Acid with PPIs, pH study findings, Histology etc make the manuscript more reader friendly.

A. We agree and have made appropriate changes.

Q. In results section, it is mentioned that grading of inflammation was stable throughout study period in Group2. However, in methods it is mentioned that group 2 had only one endoscopy.

A. We agree and have made appropriate changes.

Q. Discussion is rambling and need to be shortened presenting only relevant information for this study. Since this study is not designed to address longterm effects of acid suppression with PPIs in Barrett's, that part of discussion can be deleted.

A. We have made appropriate changes

Q. References need to be formatted per WJG guidelines.

A. Completed.

Comments on the reviewers' reports

Reviewer 3

First of all we thank this reviewer for his/her very helpful comments that we here address step-by-step.

Q 1. The number of patients participating in the two cohorts is small-however this cannot be changed. The study has been very meticulously designed and accomplished and has reached to important conclusions. However, the study is of relatively short duration. Moreover the group 2 consists of patients who had undergone a previous fundoplication in the past, so this group did not receive prospectively any further treatment, not even the subgroup of patients with abnormal acid reflux (12/30 pat).

A. We do agree but the potential advantage of the outcome in the operated BE patient resides in the possibility to compare those BE patients who had remaining duodenogastroesophageal reflux and those in whom all reflux had been eliminated. Moreover, these results reflect the difficulties in offering effective ARS in long-segment BE. We have addressed these aspects and also aspects related to the possible role of the limited time of treatment on respective dose of the PPI.

Q2. In the first cohort of medical treatment, it is interested that increasing doses of PPIs have been used to achieve reflux control. This indicates that manipulation of therapy in such a difficult-to-control disease is essential- however, this makes the results of the study more vulnerable to biases.

A. Again, we do agree that there exists a risk for bias, but we have taken serious considerations in the design and conduct of the study to blind the assessors for the group affiliation as well as the time point where the actual data were retrieved from. We also agree that there are only minor changes when titrating the PPI dose upwards further beyond the starting PPI dose. We have adjusted the discussion and conclusions accordingly.

Q3. A strong point of this study is the histological results. The authors studied the papillary length, basal cell layer, thickness and the width of the intercellular spaces. They admitted however that there was only a marginal effect of therapy towards normalization, and this is probably due to a limited time of follow up period.

A. We would like to thank this reviewer in particular for this comments. The histology was evaluated blindly by one of the biggest experts in the field. A long follow-up was not the aim of this protocol due to its detail and demanding characteristics for patients.

Q4. The study is generally acceptable and leads to useful conclusions. However, the results could be considered as preliminary of an ongoing study comparing medical to surgical treatment of GERD and the efficacy of the two treatments in preventing Barrett's esophagus.

A. We do agree and have taken this fundamental position throughout the manuscript. There are on-going studies within the field although the difficulties in designing and completing corresponding trials are substantial. We have discussed the issues related to the preventive effects of PPI as well as antireflux surgery on the development of dysplastic and neoplastic changes in BE.