Reviewer's report

Title: Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: a randomized, multicenter, open label, crossover study

Version: 1

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Reviewer: Oliver Owen Owen Koch

Reviewer's report:

Comments to the authors:

The aim of your study was to determine if transoral fundoplication (TF) could further improve clinical outcomes in partial responders to high-dose (HD) proton-pump inhibitor (PPI) therapy and to evaluate durability of TF. The answer you give after analysing the results of your study is that in "well selected patients" TF may work.

The design of the study is interesting and could show that TF can help patients with symptoms despite optimal treatment with PPI. However the results also show that TF does not help all of the patients to get free of symptoms and does not normalize esophageal acid exposure (EAE) in the majority of patients. It is a shame that you did not use HR-manometry and combined Multichannel-Impedance-pH-Monitoring in the study. Since I think using these methods you would have been able to answer questions which remain open.

Major Compulsory Revisions:

Which patients do you mean with "well selected" patients? Patients with normal LES pressure? Patients with normal esophageal motility? We do not know since HR-manometry has not been used before and after the procedure. You should state this in your limitations of the study in the discussion part. In the section “Association analysis” you show that “only preoperative total number of long refluxes < 12 stayed significantly associated with normalization of EAE”. Could this be because of preoperatively not seen poor esophageal motility and therefore poor esophageal clearance? Could you please comment.

What do you think is the pathophysiologic mechanism of the TF device? You say that you create an intact valve, but you treated patients who partly had an intact valve (Hill I). How does the device work in these patients? Could this be the reason that TF failed to normalize EAE in the majority of the patients, because you selected the wrong patients? How are the postoperative results if you analyse Hill grade I and II patients separately? Could you please comment and discuss.

Furthermore, patients whose symptoms are associated with reflux but not adequately respond to acid suppressive therapy can be identified by combined Multichannel-Impedance-pH-Monitoring. However you did not use this method,
as you comment in the discussion. In the methods section you state: “Included were patients with abnormal 48-hours ambulatory pH test defined as % time pH < 4 greater than 5.3% of the total recording period”. If all your patients had an abnormal EAE why did the PPI-Therapy not normalize the EAE in almost 50% of the patients and why did esophagitis only heal in 38% of the patients? In literature esophagitis heals in virtually all patients if they are sufficiently treated by acid suppressive medical therapy [Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial; Aliment Pharmacol Ther 2000; 14: 1249-1258] Could you please comment on this finding.

Endoscopic procedures have been criticized for normalizing esophageal acid exposure in only 30-40% of the patients treated. Esophageal 24-h pH normalization is widely considered as a crucial component of GERD treatment, because one of the goals is to avoid long-term complications. In this study using the TF device the normalization of EAE was 33% respectively 45% after 12 months, although esophagitis healed and symptoms resolved in the majority of the patients. This fact is very important considering that there is a subgroup of individuals with mild symptoms who are not willing to undergo surgery because of side effects, but seek an effective, minimally invasive therapy. From the patient’s point of view, the so-called heuristic endpoints, such as symptom resolution, duration of convalescence, patient satisfaction, well-being, and quality of life, are at least as important as the “classical” outcomes.

This study shows that endoscopic therapy can help patients with symptoms of GERD despite PPI therapy, and therefore it should be published. However there are a few lacks in the study design (Methods), and many questions remain unanswered especially which patients we should select to achieve optimal outcome.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'