

Response letter to the reviewers

Reviewer 1:

Well written manuscript. I would only suggest a few minor revisions 1 Title. - I would suggest changing the title to OUTCOMES OF PER ORAL ENDOSCOPIC PYLOROMYOTOMY IN GASTROPARESIS WORLDWIDE - Changes title as suggested

2 Abstract. - IS ADEQUATE

3 Key words. Do the key words reflect the focus of the manuscript? - ARE ADEQUATE

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? - IS ADEQUATE

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? - IS ADEQUATE

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? - IN THE ITEM PREDICTIVE FACTORS, PLEASE EXPLAIN WHAT THE TERM "ENDOFLIP" MEANS

Revisions made to add details on EndoFLIP:

Endoscopic Functional Luminal Imaging Probe (EndoFLIP) is a system which was first described in clinical practice in 2007. Impedance planimetry (IP) is a technique which allows to study the relationship of cross sectional area (CSA) and pressure during volume distention in GI lumen. EndoFLIP uses multi-detector IP system to produce 3-dimensional images of any distensible organ within GI tract ⁷¹. EndoFLIP recordings allow dynamic imaging of sphincter distention with a cylindrical balloon of variable diameter with instant cross sectional area measurement along with direct calculations of pyloric sphincter pressures ⁷². While EndoFLIP has shown to have widely useful in

esophageal disorder, it's use across other gastrointestinal motility disorder has been increasing as well ⁷¹.

8 Illustrations and tables. - TABLES ARE ADEQUATE - THERE ARE NO FIGURES IN THIS MANUSCRIPT: PLEASE INCLUDE A SERIES OF PICTURES OF THIS PROCEDURE IN THE ITEM "PROCEDURE TECHNIQUES"

Figure added:

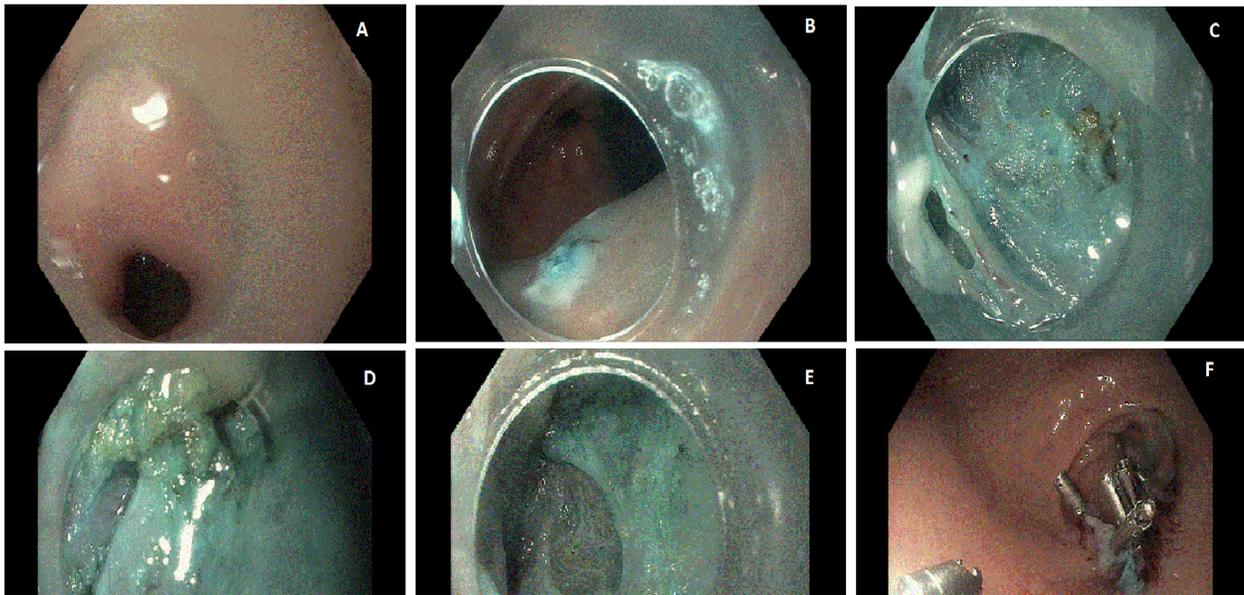


Image -1: A) Pre-pyloric area in the stomach, B) Mucosotomy site in prepyloric area, C) Submucosal tunnel creation , D) Pyloric ring, E) Myotomy, F) Closure of mucosotomy site with endoclips

11 References. - ADEQUATE

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? - IS ADEQUATE

Reviewer 2:

Treatment of gastroparesis is an actual problem of modern gastroenterology. It is often chronic and debilitating as medical treatments, including promotility agents, are only modestly effective at controlling symptoms. Interventional therapeutic modalities such as gastric electrical stimulation, laparoscopic pyloroplasty, or gastrostomy may be considered for patients with medically refractory gastroparesis. However, those interventions are either too invasive or not very effective. Recently, there has been a tremendous interest in minimally invasive gastric drainage procedures aimed at the pylorus. Khashab et al. performed the first gastric peroral endoscopic pyloromyotomy (G-POEM) in 2013, without any adverse events and with significant improvement in patient's symptoms after 12 weeks of follow-up. The review presented by the authors summarizes the existing data on the clinical outcome of per oral endoscopic pyloromyotomy (POP or G-POEM). They showed that POP is a safe and effective method of treating patients with refractory gastroparesis. However, their findings are mainly based on the results of retrospective studies, which is a significant limitation. Indeed, larger series and multicenter trials with a prospective design are required. They should focus on optimal patient selection and factors that are associated with positive response.

We definitely agree that most data on outcomes of GPOEM are currently derived from the retrospective studies. The intent of this review article was to compile the current outcome data on GPOEM. We did include the studies which has showed some predictive factors after GPOEM. Malik et al. showed prior response to Botulinum toxins in pylorus is a positive predictive factor after GPOEM. Rodriguez et al. has shown idiopathic and post-surgical gastroparesis has better outcomes as compared to diabetic gastroparesis while Mekaroonkamol et al. showed shorter duration of disease has better outcomes after GPOEM. Malik et al. used EndoFLIP showing increase in cross sectional area of the pylorus was associated with favorable outcome after GPOEM. While these are some factors derived from various retrospective studies, there are few ongoing

prospective studies currently including few at our center addressing question of proper patient selection for this procedure. As outlines in conclusion section of our manuscript, there are definite limitations in the current data on GPOEM and future large, possibly multicenter prospective trials are needed to further enhance understanding in selecting appropriate patients for this intervention. Hopefully, some of the ongoing trials will provide such information in near future.

Reviewer: 3

Dr. Mekaroonkamol, et al. reviewed 'Global Outcomes of Per Oral Endoscopic Pyloromyotomy in Gastroparesis'. The manuscript is informative and well-presented.

Comments

1. Please describe the diagnosis methods of gastroparesis.

Segment added in the introduction:

The three main etiology cited for gastroparesis include Idiopathic, diabetic related and post-surgical. Gastroparesis clinically manifests as recurrent postprandial nausea and vomiting, early satiety post prandial bloating and upper abdominal pain ². In severe cases, it can also lead to weight loss and malnutrition ³. The diagnosis of gastroparesis is suspected by constellation of these clinical symptoms. The diagnosis is further confirmed based on normal upper endoscopy ruling out any structural obstruction and 4 hour gastric emptying study proving impaired gastric emptying ²

2. Please describe the adaptation of POP.

Segment added to the introduction.

With the significant advancement in the field of submucosal endoscopy in last few years, Per Oral Endoscopic Pyloromyotomy (POP), also known as Gastric Per Oral Endoscopic myotomy (GPOEM), has emerged as a pylorus-directed

therapy for gastroparesis. The approach is derived from similar concept of per-oral endoscopic myotomy (POEM) of lower esophageal sphincter for achalasia ³⁶. POP improvises the submucosal endoscopy technique, similar to what is used for POEM in achalasia, to identify and dissect the pyloric muscle. The procedure is performed in the safety of submucosal tunnel thus offering a less-invasive approach for pyloromyotomy.³⁷⁻³⁹. This novel minimally-invasive endoscopic procedure with its promising outcomes has quickly gained popularity worldwide. The first human case of POP was performed by Khashab et al. in 2013 without any adverse event and significant clinical improvement at 12 weeks follow up ³⁹. Subsequently in 2014 first human case of POP was performed successfully in Europe and subsequently in 2015 a case series of 7 patients was published on POP outcomes in humans ³⁷. Since then, many single center and few multicenter studies have been published reporting short term outcomes on POP in gastroparesis patients, mostly in retrospective fashion (Table-1)