

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name "Revised manuscript").

Title: The Role of Balloon Enteroscopy for Obscure Gastrointestinal Bleeding in Those with Surgically Altered Anatomy: A Systematic Review

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Name of Journal: World Journal of Gastrointestinal Endoscopy

Manuscript ID: 74938

Manuscript Type: Systematic Review

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We emended the paper according to the reviewers' comments. We hope this revision will make our manuscript better to be accepted in your journal.

Each comment has been answered accordingly in the manuscript. We hope that the revised version will fulfill the requirements for publication in the World

Journal of Gastrointestinal Endoscopy.

Thank you very much

Reply to editorial comments:

Reviewer 1

Obscure gastrointestinal bleeding is difficult to diagnose and treat. This systematic review analyzes the diagnostic value and safety of balloon enteroscopy in obscure gastrointestinal bleeding. This review indicates that the data on the clinical utility of balloon enteroscopy in the evaluation of small bowel bleeding remains limited in those with surgically altered anatomy. Although balloon enteroscopy represents diagnostic and therapeutic yields as high as 83% and 64% respectively, its incidence of perforation as high as 7%. In addition, the number of studies included in this paper is small and it still needs to be further improved, such as inclusion criteria and exclusion criteria.

- Thank you for the comment. As indicated in our methods section, we performed an extensive literature review across multiple databases by searching through over 500 pieces of literature. The references of these papers were also analyzed to ensure our search was all inclusive. We went back and performed our literature search once again amongst the multiple search platforms and did not find any additional studies to fit our inclusion criteria. Our study is ultimately limited by the lack of clinically relevant literature to fit our inclusion criteria; however, this highlights the need for further studies to better investigate the role of balloon enteroscopy in surgically altered anatomy patients as a whole. This was further touched upon in our discussion: "The lack of extensive literature that fits our inclusion criteria highlights the need for further studies to continue to assess the role of balloon enteroscopy in surgically altered anatomy patients."

Reviewer 2

The authors presented the systematic review to assess the diagnostic and therapeutic yield of balloon enteroscopy for obscure gastrointestinal bleeding in patients with altered surgical anatomy. However, there are some points to be considered and revised in the manuscript as below.

1. The results of this manuscript may be misleading and need to be reconsidered because there are several case reports in the selected reports with success rates of 100% for diagnosis and treatment with no adverse events.
 - a. Thank you for the comment. We understand this is a limitation to our study and added further explanation in our limitations paragraph of the results section: "Given the limited availability of studies to fit our inclusion criteria, we included case reports which may have skewed our overall results given many having 100% diagnosis rates and 0% complication rates."
2. In the systematic review of BAE-ERCP in patients with altered surgical anatomy (Anvari S, et al. Surg Endosc. 2021; 35: 18-36., Tasisaka Y, et al. Dig Endosc. 2021; 33: 1034-44.), the perforation rate is around 1%, but in this paper, it is shown to be 7-8%. It would be better to discuss why it is different.
 - a. Thank you for the comment. A paragraph was added to the discussion which includes systematic reviews of BAE-ERCP and compares their results to our findings. "When compared to previous systematic reviews of balloon assisted ERCP in those with surgically altered anatomy, our study has notable differences. Diagnostic yields have varied between 70-90% with procedure success rates approaching 62-93% amongst single or double balloon assisted ERCP. [37-39] These studies depicted overall

adverse events rates between 4-7% with perforations making up a minority of these complications. [37-39] Such variance from our study may stem from the purpose of procedure with balloon enteroscopy for obscure GI bleeding requiring a thorough investigation of the small bowel where balloon assisted ERCP typically focuses on assessment and interventions within the biliary tree. Although both procedures can be technically challenging, underlying maneuvers and interventions can vary. The higher incidence of perforation rate in our study when compared to balloon assisted ERCP may be attributed to aspects related to altered anatomy including procedure time, more extended exploration of the small bowel, presence of underlying adhesions and different targeted therapeutic techniques. Further studies are needed to further characterize these differences.”

3. It would be better to assess the differences of treatment outcome between the transoral and the transanal approach.
 - a. Thank you for the comment. We agree that this would be a useful and interesting assessment; however, the studies that fit our inclusion criteria do not adequately comment on retrograde versus anterograde approaches to allow us to form an assessment. This was included in our limitations paragraph: “Furthermore, we were unable to perform analysis based on the procedure approach (retrograde vs anterograde) given reporting variability amongst the studies.”

4. The perforation rate is noted as 8% in the discussion, but as 7% in the conclusion.
 - a. Thank you for the comment. The perforation rate in the discussion was corrected to 7%.

In the manuscript “The Role of Balloon Enteroscopy for Obscure Gastrointestinal Bleeding in Those with Surgically Altered Anatomy: A Systematic Review”, the authors assessed the safety and diagnostic efficacy of balloon enteroscopy for obscure GI bleeding in patients with altered surgical anatomy. The authors extracted data through PubMed, MEDLINE, Google Scholar, Scopus, and Embase with the key words “enteroscopy,” “obscure bleeding,” and “altered anatomy,” that fit inclusion criteria. Forty-four (65%) of the procedures were double balloon, 21 (31%) were single balloon (SBE), and 3 (4%) was classified as through the scope balloon assisted. The most common altered anatomy types included Gastric bypass Roux-en-Y (GBR), Pylorus sparing Whipple (PSW), Orthotopic Liver Transplantation with Roux-en-Y (OLTR), and Gastrojejunostomy Roux-en-Y (GJR). There were 5 (7%) procedures that were complicated by perforation. The diagnostic yield was 48/59 (81%) and a therapeutic yield of 39/59 (66%). Though this work is interesting, some issues rise. Major issues:

- 1, The numbers of the included literatures and the included cases are too limited.

- Thank you for the comment. As indicated in our methods section, we performed an extensive literature review across multiple databases by searching through over 500 pieces of literature. The references of these papers were also analyzed to ensure our search was all inclusive. We went back and performed our

literature search once again amongst the multiple search platforms and did not find any additional studies to fit our inclusion criteria. Our study is ultimately limited by the lack of clinically relevant literature to fit our inclusion criteria; however, this highlights the need for further studies to better investigate the role of balloon enteroscopy in surgically altered anatomy patients as a whole. This was further touched upon in our discussion: “The lack of extensive literature that fits our inclusion criteria highlights the need for further studies to continue to assess the role of balloon enteroscopy in surgically altered anatomy patients.”

2, The comparison of the role of balloon enteroscopy between surgically altered anatomy and common anatomy should be given.

- Thank you for the comment. We expanded one of our paragraphs to first touch upon the role of balloon enteroscopy for obscure GI bleed in those with common anatomy. We added several references to discuss diagnostic yield and potentially adverse events. The paragraph then transitions to the emerging role of balloon enteroscopy in those with surgically altered anatomy. Obscure GI bleeding has been estimated to account for 5-10% of all GI bleeding, with increasing number of patients requiring balloon enteroscopy for small bowel evaluation [25]. The diagnostic yield of balloon enteroscopy amongst those without altered anatomy has been reported around 45-55%. [26-27]. Adverse rates are overall low at 3.2% with most common complications including intestinal bleeding, perforation, or post-procedure pancreatitis. [28-29]. With the emerging surgical techniques for various GI pathologies, surgically altered GI anatomy remains prevalent. The obesity epidemic in the United States has led to

increased referrals to bariatric surgeries. Additionally, the advancements in liver transplant (LT) have led to increasing number of patients receiving LT over the past several years. [25] Given their surgically altered GI anatomy, these patients remain at risk for GI bleeding. Furthermore, the management of these patients may be complicated by surgical anastomotic sites often serving as culprits of obscure GI bleeding. [7, 26-27] These patients may require work up leading to SBE or DBE for underlying diagnosis.”

3, please compare the roles of balloon enteroscopy between different surgically altered anatomy types, and give explanation how different surgically altered anatomy types affect the roles of balloon enteroscopy.

- Thank you for the comment. We included more reported findings in the results section regarding altered anatomy type with perforation frequency. “Amongst the 5 reported procedure related perforations, 2 (40%) patients had a Rou-en-Y. The remaining 3 patients consisted of an ileal-sigmoid anastomosis, a right hemicolectomy with ileostomy, and an unspecified altered anatomy type.”
- Additionally, we included another paragraph in the discussion touching upon this further “GBR, PSW, OLTR, and GJR were the most reported altered anatomy types observed in our review. The various types of altered anatomy structures may have an impact on the underlying procedure regarding luminal passage and scope maneuvers. No trend was identified regarding an association between diagnostic or therapeutic yield with altered anatomy types. We observed that 20% of the observed perforations were seen in patients with a Roux-en-Y. Those with

altered small bowel anatomy may be more prone to suffer procedure related complications; however, further work is needed to verify these findings.”

4, Regarding the complications, only perforation was mentioned. Is there any other complication?

- Thank you for the comment. No other complications were mentioned consistently throughout the literature.

Minor issue Fig2,3,4, the authors should give the corresponding references.

- Thank you for the comment. These are original images taken from our institution and are not associated with any of the cited papers. We obtained permission and informed consent from these patients to include these images in our manuscript.

Science Editor

The authors present a systematic review to evaluate the efficacy of balloon enteroscopy in the diagnosis and treatment of unexplained gastrointestinal bleeding in patients with surgical anatomical changes. The manuscript has some clinical value, but it is not good enough.

The manuscript did not include enough literature and relevant cases, and there were not many adverse reactions.

- Thank you for the comment. As indicated in our methods section, we performed an extensive literature review across multiple databases by searching through over 500 pieces of literature. The references of these papers were also analyzed to ensure our search was all inclusive. We went back and performed our literature search once again amongst the multiple search platforms and did not

find any additional studies to fit our inclusion criteria. Our study is ultimately limited by the lack of clinically relevant literature to fit our inclusion criteria; however, this highlights the need for further studies to better investigate the role of balloon enteroscopy in surgically altered anatomy patients as a whole. This was further touched upon in our discussion: “The lack of extensive literature that fits our inclusion criteria highlights the need for further studies to continue to assess the role of balloon enteroscopy in surgically altered anatomy patients.”

Figure legend is very simple.

- Thank you for the comment. The figure legends were expanded with further details.

The format of the table should use a three line table.

- Thank you for the comment. The table was formatted to a three-line table.

Company Editor-in-Chief

I recommend the manuscript to be published in the World Journal of Gastrointestinal Endoscopy.

- Thank you for the comment.