

Cover letter

Manuscript NO: 46828

Dear Editor of *World Journal of Gastroenterology*,

We would like to thank you and the reviewers of our manuscript for careful review and comments. We have made some corrections following your helpful comments, and we believe our paper has been much improved as a result.

Therefore, we would like to resubmit this revised manuscript entitled “Recent advances in ERCP in Billroth II gastrectomy patients: A systematic review” by Tae Young Park and myself to the “*World Journal of Gastroenterology*” for publication. A point-by-point response to the comments of reviewers is also provided. All authors agreed to accept equal responsibility for the accuracy of the content of the paper.

We hope the revised manuscript will better meet the requirements of the “*World Journal of Gastroenterology*” for publication and be finally accepted.

We thank you again for your thoughtful considerations.

Sincerely yours,

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Point-by-Point Response

To Editor

Please don't include abbreviations in the title.

Response: We corrected our manuscript in “Cover page” as follows:

From) Recent advances in ERCP in Billroth II gastrectomy patients: A systematic review

To) Recent advances in Endoscopic retrograde cholangiopancreatography in Billroth II gastrectomy patients: A systematic review

Please provide the postcode.

Response: Postcodes are provided as follows:

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The 5 sections of the structured abstract are: Background, Aims, Methods, Results, and Conclusion. This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis. Please write your research background.

Response: Authors appreciate your helpful comment. We added a paragraph to our manuscript in the “Abstract” section as follows:

“BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) in patients with Billroth II gastrectomy has been considered a challenging procedure due to the surgically altered gastrointestinal anatomy. However, there has been a paucity of comparative studies

regarding ERCP in Billroth II gastrectomy cases because of procedure-related morbidity and mortality and practical and ethical limitations. This systematic and comprehensive review was performed to obtain a recent perspective on ERCP in Billroth II gastrectomy patients.”

4. Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. The purpose of the Core Tip is to attract readers’ interest for reading the full version of your article and increasing the impact of your article in your field of study.

Response: The Core Tip is provided as follow:

“Endoscopic retrograde cholangiopancreatography (ERCP) in Billroth II gastrectomy anatomy has been considered a difficult procedure due to the surgical alteration. To date, there has been a paucity of comparative studies regarding ERCP in Billroth II gastrectomy patients. In current study, we systematically and comprehensively reviewed the literatures regarding ERCP in Billroth II gastrectomy cases. The performance of ERCP in the Billroth II gastrectomy has been improving with choice of various type of endoscope and sphincter therapy. More comparative studies are required to perform effective and safe ERCP in Billroth II gastrectomy population.”

5. Please offer the audio core tip, the requirement are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article.

Response: Audio core tip file has been submitted as you indicated.

6. The guidelines for writing and formatting Article Highlights are as follows:

Response: Article highlights were provided as follows:

(1) ***Research background***

Endoscopic retrograde cholangiopancreatography (ERCP) in patients who have a Billroth II gastrectomy has been considered a difficult procedure due to the surgically altered anatomy. The difficulties of ERCP in patients with Billroth II gastrectomy include the intubation of the afferent loop, visualization of the papilla, selective cannulation of the bile duct, and optimal sphincter management due to the reverse direction of the papilla. To perform safe and effective ERCP in Billroth II gastrectomy cases, considerable efforts have been put in several ways including the choice of endoscope and sphincter management. However, there has been a paucity of comparative studies on the efficacy and safety regarding ERCP in Billroth II gastrectomy.

(2) ***Research motivation***

At present, comparative studies on the efficacy and safety of ERCP in Billroth II gastrectomy cases are lacking because of practical and ethical limitations due to procedure-related morbidity and mortality. This systematic and comprehensive review was performed to obtain a recent perspective on ERCP in Billroth II gastrectomy patients.

(3) ***Research objectives***

The main objective of the study was to assess the efficacy and safety of ERCP in Billroth II gastrectomy patients. In detail, the assessment of success rate of afferent loop intubation and selective cannulation, and rate of adverse events including bowel perforation, post-ERCP pancreatitis, bleeding, cardiopulmonary events, and mortality was performed. In addition, the assessment of these outcomes according to each type of endoscopy and sphincter management methods was performed.

(4) ***Research methods***

A systematic review was performed on the literatures that evaluated the outcomes of ERCP in Billroth II gastrectomy patients. Electronic databases were searched, including PubMed, EMBASE, and Cochrane Library. The outcomes of afferent loop intubation and selective cannulation, and occurrence of adverse events were assessed.

(5) *Research results*

A total of 43 studies involving 2669 patients were included. The overall success rate of afferent loop intubation was 91.3% (2437/2669), and the overall success rate of selective cannulation was 87.9% (2346/2437). A total of 195 cases (7.3%) of adverse events occurred. Bowel perforations occurred in 74 cases (2.8%), post-ERCP pancreatitis in 65 cases (2.4%), bleeding in 37 cases (1.4%), mortality in 9 cases (0.3%).

(6) *Research conclusions*

This systematic review showed that the performance of ERCP in the Billroth II gastrectomy patients has been improving with choice of endoscope and sphincter management. To determine the optimal method to perform safe and effective ERCP in Billroth II gastrectomy patients, more comparative studies are needed in the future.

(7) *Research perspectives*

The success of ERCP in Billroth II gastrectomy has been improving with technical advance. Future research is needed to explore the optimal approach in performance of ERCP in Billroth II gastrectomy cases.

Please check and confirm that there are no repeated references! Please add PubMed citation numbers (**PMID** NOT PMCID) and DOI citation to the reference list and **list all authors**. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

Response: Authors confirm that there are no repeated references. PubMed citation numbers (PMID NOT PMCID) and DOI citation were provided. And, the first page of the paper without PMID and DOI was provided as supplementary file separately.

Please don't include any *, #, †, §, ‡, ¥....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters.

Response: We corrected our manuscript as follows:

From) *Cap-fitted forward-viewing endoscope

To) ¹Cap-fitted forward-viewing endoscope.

Please provide the decomposable figure of figures, whose parts are all movable and editable.....must be editable. Please provide the text in your figure(s) in text boxes.

Response: Editable PPT file of the figures were submitted on the system as follows as you requested:

To Reviewer 03646569

Comments

The systematic review by Park et al provides detailed information about all available endoscopic approaches for ERCP in Billroth II gastrectomy patients. The purpose is to systematically review the available literature regarding this topic including the advantages, success rates and adverse events of different endoscopic techniques. ERCP in BII patients remains a challenging procedure despite the advances in the endoscopic therapy and still not all the problems are solved.- this was also discussed by the authors. The article provides useful information about the current status and highlights the need for further development in the area.

Response: Authors agree with your opinion. To date, there has been a paucity of comparative studies regarding ERCP in Billroth II gastrectomy cases because of procedure-related morbidity and mortality and practical and ethical limitations. To assess the efficacy of ERCP in Billroth II gastrectomy patients by afferent loop intubation and the selective cannulation as well as the adverse events including bowel perforation, post-ERCP pancreatitis, bleeding, cardiopulmonary events, and mortality, we systematically and comprehensively reviewed the literatures.

To Reviewer 03475260

Comments

In this systematic review, Park and Song aimed to analyze the available evidence on ERCP in patients with Billroth II gastrectomy. The final analysis included 43 studies and 2669 patients, and reported data about successful afferent loop intubation, successful cannulation of the desired duct and adverse events, as well as information about the endoscope used and sphincter management methods. This is an interesting review on an important topic, nevertheless several points need to be further discussed to allow a correct interpretation of the data.

Major points:

- In the abstract conclusion, the Authors stated that “The performance of ERCP in the Billroth II gastrectomy population has been improving with the advent of novel endoscopic instruments and advanced techniques”. However, in the manuscript it is not clearly described a trend toward a better outcome with novel technologies. Moreover, despite the title of the manuscript, the “recent advances” in this field have not been sufficiently detailed. These points should be further discussed.

Response: Authors appreciate your excellent comment. Unfortunately, we failed to describe a trend and outcome of specific novel technologies in ERCP in Billroth II gastrectomy. Because most of studies regarding novel technologies were case report, case series, and animal study, they were excluded from current systematic review. These points are major limitation of current study. Therefore, we have corrected our manuscript in the “Abstract-conclusion” section as follows:

From) “The performance of ERCP in the Billroth II gastrectomy population has been improving with the advent of novel endoscopic instruments and advanced techniques. More comparative studies are needed to determine the optimal strategy to perform safe and effective ERCP in Billroth II gastrectomy patients.”

To) “The performance of ERCP in the Billroth II gastrectomy population has been improving with choice of various type of endoscope and sphincter management. More comparative studies are needed to determine the optimal strategy to perform safe and effective ERCP in Billroth II gastrectomy patients.”

And, we also have added a paragraph to our manuscript in the “Discussion-limitation” section as follows:

“In this study, it is not sufficiently and clearly described a recent trend toward a better outcome with novel technologies in ERCP in Billroth II gastrectomy patients. Because most of studies regarding novel technologies were case report, case series, and animal study, they were excluded from current systematic review. This point is major limitation of current study.”

- Despite this work aims to analyzed Billroth II patients, the Authors included several cases of different surgical altered anatomy (Pancreaticoduodenectomy, Roux-en-Y gastrectomy, Hepaticojejunostomy with Roux-en-Y, as reported in table 1 and table 2). This should be clearly explained in the title, abstract and manuscript, as different surgical reconstructions may have different outcome in ERCP. Alternatively, these cases should be excluded from the analysis.

Response: Authors agree your suggestion. Cases of different surgical altered anatomy was excluded from the analysis, and their data were removed from the manuscript.

- Since different indications for ERCP may have different outcome in terms of cannulation rate or adverse events (e.g. malignant stenosis vs bile duct stones), data about ERCP indication, if available, should be provided, or, alternatively, the Authors should comment this aspect.

Response: Authors appreciate your comment. Detailed data of indications for ERCP were provided in Table 1.

- The Authors reported afferent loop intubation rate and cannulation rate. Are data about procedure clinical success (e.g. stones clearance, successful stent placement) available?

Response: Authors agree with your helpful comment. This current systematic review mainly focused on the afferent loop intubation rate and cannulation rate because the first concern in performing ERCP in Billroth II gastrectomy cases is technical success including selective afferent loop intubation rate and selective bile or pancreatic duct cannulation. If afferent loop

intubation and selective cannulation were achieved, most of procedures can obtain the planned therapeutic goals including stone removal endobiliary biopsy sampling, internal or external biliary drainage.

- The Authors reported a graphic representation of different Billroth II reconstructions after gastrectomy. If data about difference of ERCP outcome between different surgical reconstructions are not known or not available, consider to remove the figure, as potentially confounding.

Response: Authors agree with your opinion. The data about outcomes of ERCP between different Billroth II reconstructions not available. Therefore, graphic representation of the type of Billroth II gastrectomy is removed.

- The Authors reported a “Subgroup analysis according to the sphincter management methods”. Sphincter management is supposed to affect clinical efficacy of the procedure rather than cannulation rate or afferent loop intubation rate. Please expand these findings reporting clinical outcome according to this subgroup analysis.

Response: Authors agree with your opinion. Clinical outcomes according to the sphincter therapy was also evaluated. The result was provided in Table 5 and we added sentences to our manuscript as follows:

“INTRODUCTION” section

3) to assess clinical efficacy according to each type of sphincter management methods.

“MATERIAL AND METHODS” section

And clinical outcomes according to the type of sphincter therapy was also evaluated. Clinical success was defined as the achievement of the planned therapeutic goals including bile duct stone clearance, endobiliary biopsy, biliary stent or nasobiliary catheter insertion.

“RESULTS-Subgroup analysis” section

“The clinical success rates of achievement for the planned therapeutic goals according to the sphincter management ranged from 85.8% to 93.6%.”

7- Please provide more details about the use and the potential advantages of dual lumen endoscope in this setting.

Response: We added a paragraph to our manuscript in the “Discussion” section as follows:

“The use of dual lumen endoscope has potential advantage that the cooperation of two instruments through different channels can facilitate papillary cannulation in cases with difficult anatomy such as periampullary diverticulum and surgical altered anatomy.”

Minor revisions:

- In the manuscript there are some typing errors (e.g. in the text of fig. 4). Please revise the manuscript and amend the errors.

Response: We corrected our manuscript as follows:

From) **Figure 4** Cap-fitting forward-viewing endoscopy A: Naïve papilla; It is difficult to obtain en face view. The direction of bile duct is reversed (arrow).

To) **Figure 3** Cap-fitting forward-viewing endoscopy A: Naïve papilla; It is difficult to obtain en face view. The direction of bile duct is reversed (arrow).

To reviewer 01467632

Comments

Park and Song conducted a comprehensive systematic review on ERCP performed on BII patients, evaluating the possible scopes that can be used and evaluating rate of afferent loop intubation and biliary cannulation and complications based on the scope. Three electronic databases were searched and 43 studies finally analyzed for a total of 2669 patients included. The review is methodologically well performed, well written and interesting in content. The discussion is well written and interesting for the reader and raises the need of further studies to be performed. I suggest the article to be published in this form as, in my opinion, there are no revisions to be made.

Response: Authors appreciate your comment. The results of this systematic review can provide information between the various types of endoscopes and sphincter management for ERCP in Billroth II gastrectomy patients, which would be ethically and practically difficult to perform a randomized controlled trial. This systematic review also showed that the performance of ERCP in the Billroth II gastrectomy patients has been improving with choice of endoscope and sphincter management. A randomized controlled trial is needed to confirm the superiority between the types of endoscopes and sphincter management for ERCP in patients with Billroth II gastrectomy in the future.

To reviewer 03271124

Comments

Dear author, The manuscript entitled “Recent advances in ERCP in Billroth II gastrectomy patients: A systematic review” is well written. Comments, 1. The previous studies included in this systematic review are relatively wide range (from 1984-2018) and only three studies were published in recent years. This would be the limitation of this study. Because of there are the difference of the endoscopic instruments and skill of the endoscopist between the past and the present.

Response: Authors agree with your opinion. The many of studies analyzed in current systematic review are wide range from 1984-2018, and older studies can lead to bias secondary to the technological advance, experience of endoscopists, and knowledge in performing ERCP of Billroth II gastrectomy patients. Therefore, we have added a paragraph to our manuscript in the “Discussion-limitation” section as follows:

“The older studies can lead to bias because there are the difference of the technological

advance such as endoscopic instruments and skill, overall knowledge and experience of endoscopists in performing ERCP of Billroth II gastrectomy patients between the past and the present.”