Author's response to reviews

Title: Bilio-Entero-Gastrostomy: prospective assessment of a modified biliary reconstruction with facilitated future endoscopic access.

Authors:

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Author's response to reviews: see over
Dear Sir,

On behalf of my co-author and myself, I would like to thank the editors and the reviewers for their valuable comments on our work. I am pleased to submit the "revised manuscript" of the paper considering the reviewers' reports.

Reviewer number 1: Dr. Aude Vanlander

- We would like to thank the reviewer for his interesting remarks and for stating that "the general idea and concept of the article is very interesting. It could have a potential benefit and clinical relevance in some cases to have a bilio-entero-gastrostomy. It is an article whose findings are important to those with closely related research interest."

- Regarding the design of the study:

  It is a "consecutive case series" which is a clinical study that includes all eligible patients identified by the researchers during the study registration period. The patients are treated in the order in which they are identified without control group. In our case, all eligible patients for whom hepaticojejunostomy was indicated during the study period were offered BEG shunt and followed up and tested for endoscopic access to the bilioenteric anastomosis.

- Regarding the number of patients that were included in the study:

  We would like to elucidate that this is a continuing study intended for a period of seven years. These results with that number of patients represent the enrolled patient until the date of submission of the manuscript. Further patients will be enrolled in the future till the end of the study period.

- Regarding the type of reconstruction decided:

  It was an evolving process. We began with the BEG type I. When the endoscopist faced difficulty with this technique, we modified the reconstruction to the BEG type II which appeared to be easier for the endoscopist. However, BEG type II was more complex to be performed surgically. Consequently the technique was modified to BEG type III which was not only the simplest to perform surgically but also the easiest for the
endoscopist to reach the anastomosis. This may explain the sequence of cases in relation to the type of BEG, the increased number of BEG type III and the concentration of the cases with this type toward the later period of the study. Consequently, toward the end of the study, we decided to perform all cases using BEG type III. A paragraph was added to the methods section to stress upon these data.

- Regarding the articles with similar ideas that we compared our results with:

To our knowledge, three articles in the literature were testing gastric access loop for endoscopic approach to the biliary shunt (ref. 20, 21, 22). We discussed these articles according to the available information in them. Some of these data were deficient or even absent. Nevertheless, according to the reviewer remarks, we modified the paragraph which discusses this comparison to be as clear as possible.

- Regarding the other therapeutic options that are offered to patients with benign biliary stricture in our center:

Less invasive options are usually first thought of as PTC and/or ERCP dilatation or stenting. Surgical reconstruction is only offered if the other options are either not applicable or not successful. According to the reviewer remarks, we reformulated the first paragraph of the "methods" section to stress this information.

- Regarding the minor specific revisions:

1. Abstract:

The word "shunt" in the background paragraph was changed into "anastomosis".

In the results paragraph, we mentioned the type of BEG performed for the patient who died of myocardial infarction. We also repeated that in the result section of the article manuscript.

Regarding the patient with anastomotic stricture who received endoscopic dilatation and stenting, BEG type I reconstruction was performed for that patient. This information was added to the result paragraph of the abstract.
In the "results" section of the abstract, we stated that "type III BEG was simpler to perform, faster to access endoscopically, easier and with no failure". **Simpler**: as it requires the performance of only three anastomoses in comparison to five anastomoses for each of type I and II. We changed the expression to "surgically simpler", **Faster to access**: as the time needed to reach the biliary anastomosis endoscopically was shorter for BEG type III in relation to type I and II. After reaching the biliary anastomosis, the time of the rest of the endoscopic procedure is not dependent upon the construction type. **Easier**: as the difficulty scores given by the endoscopist were consistently less for BEG type II in relation to type I and II. However, we agree with the reviewer that the cases are few and different in number to draw solid conclusion in this regard. Consequently, we changed the sentence in that paragraph to stress that these results are preliminary and represent tendency rather than solid conclusion.

Regarding the difficulty score of the endoscopic procedure, we agree with the reviewer that this score is subjective. That is why we measured the time needed to reach the biliary anastomosis which is an objective parameter of difficulty. Cases with BEG type III showed the tendency for shorter time needed to access the biliary anastomosis endoscopically. Regarding the learning curve, our endoscopist (HE) has more than fifteen year experience in gastrointestinal endoscopy including ERCP and therapeutic endoscopy. Additionally, the technique requires end-view endoscope which is much easier than the side-view endoscopy of ERCP. Although a procedure related learning curve might be considered, it was obvious to the endoscopist and also from the time required to reach the biliary anastomosis that the difficulty and elongated time were related to the type of BEG reconstruction rather than the number of procedure performed. That was apparent from the sudden and consistent drop in difficulty score and in time from the first case of BEG type III. The difficulty in type I and II was related primarily to the presence of more than one lumen from the site of enterogastrostomy on (please refer to the diagrams) which confuse the endoscopist about which lumen he should enter to reach the biliary anastomosis. This is not the case for BEG type III
which offer just one lumen at the enterogastrostomy with easier less complex endoscopic entry. A paragraph was added, in the method section of the article manuscript, to explain the evolution of the three BEG types and the difficulties faced by the endoscopist and the surgeon for each type. Another paragraph was also added to state the experience of the endoscopist.

2. Introduction:

The defined word "stricture" was changed into the word "stenosis"

An "a" was added at the requested position.

The comment on PTC as highly invasive was mentioned in the context of management of strictured surgical hepaticojejunostomy (not benign biliary stricture). That is why PTC was regarded invasive in relation to ERCP but, of course, not in relation to surgery which is far more invasive. The word "highly" was omitted. On the other hand, for management of benign biliary stricture, the treatment options offered are ERCP, PTC or surgical reconstruction. The indications for surgery were stressed in the reformulated paragraph in the beginning of the "methods" section as we stated before in response to a previous comment of the reviewer.

3. Materials and methods:

Regarding the choice of BEG type of reconstruction, a whole new paragraph in this section of the article was added to elucidate this manner as we mentioned in response to a previous comment of the reviewer.

We used 4-0 size suture for all bilioenteric anastomosis regardless of the size of the bile ducts. However, we think that 3-0 size could be suitable too.

Regarding the technique of hepaticojejunostomy, we tried to illustrate the details of the whole surgical technique as much as possible for those who are interested to know which technique we used.

Postoperatively, we used antibiotic for five days. We added this information to the text.
Regarding scoring the amount of bile in the stomach, we agree with the reviewer that these data are endoscopist dependent. However, it could throw some light on this potential complication of the technique. Nevertheless, it is not proved if the mere presence of bile in the stomach is related to clinically manifest gastritis.

4. Results:

We modified the comment on table 6 to stress upon the idea that these results are preliminary and that they represent tendency rather than solid conclusion. This was also mentioned in details in response to a previous comment by the reviewer.

5. Discussion:

In those two references, they used a reconstruction is nearly similar to BEG type III. This was stated in the next paragraph.

6. Figures:

- Picture figures were associated, whenever felt helpful, with illustrative diagrams to be more clear.

- Figure 6 was wrongly missed. We added it in the revised manuscript.

7. Tables:

- Table 2: regarding liver function data, we agree with the reviewer that these data is less important except that it shows that, in benign biliary stricture cases, the alkaline phosphatase is elevated in all cases even if the bilirubin is normal. Regarding cholangiography, the table shows the number of procedures and patients for each type of cholangiography. Also, all patients had at least one cholangiography. A slight modification was done for this table in the cholangiography sector.

- Table 5: regarding the difficulty score, this was extensively discussed in response to a previous comment of the reviewer.
Finally we would like to thank the respected reviewer for his obvious interest and valuable remarks that led us to modify our manuscript in a way to be, we hope, more clear and beneficial.
Reviewer number 2: Dr. Reza F Saidi:

We would like to thank the reviewer for his interesting remarks and for stating that "the idea is important and the article is of importance in its field."

1. Regarding for the rational and selection criteria of the three types of BEG reconstruction, it was an evolving process. We began with the BEG type I. When the endoscopist faced difficulty with this technique, we modified the reconstruction to the BEG type II which appeared to be easier for the endoscopist. However, BEG type II was more complex to be performed surgically. Consequently the technique was modified to BEG type III which was not only the simplest to perform surgically but also the easiest for the endoscopist to reach the anastomosis. This may explain the sequence of cases in relation to the type of BEG, the increased number of BEG type III and the concentration of the cases with this type toward the later period of the study. Consequently, toward the end of the study, we decided to perform all cases using BEG type III. A paragraph was added to the methods section to stress upon these data.

2. We agree with the reviewer that the long time effect of biliary reflux is unknown and needs longer follow up to be addressed.

3. Regarding recurrent cholangitis after BEG:

   We used Terblanche clinical grading to assess the clinical results (see table 1). In table 4, we showed the postoperative results during the follow up period. There were one patient with grade III and one with grade IV; both (12.5%) had recurrent cholangitis by definition and the last one required endoscopic dilatation and stenting of the biliary anastomosis facilitated by BEG reconstruction.

4. We agree with the reviewer that the difficulty score is endoscopist-dependent. That is why we measured the time needed to reach the biliary anastomosis which is an objective parameter of difficulty to compensate for the subjectivity of the difficulty score.

5. Regarding the reasoning to change from BEG types I and II to BEG type III, this was illustrated through the answer for the question number 1.
Finally we would like to thank the respected reviewer for his valuable remarks that helped us to make the article, hopefully, more valuable.
Reviewer number 3: Dr. Geert Roeyen:

We would like to thank the reviewer for his important remarks.

- Regarding the tables and figures, we tried to be as illustrative as possible to throw enough light on the data and the surgical technique.

- Regarding the use of balloon enteroscopy, whether double or single, we have already discussed these techniques in the 2nd paragraph of the "discussion" section. We referred the reader to reference 13 and 14. These methods are still under evolution and assessment. We do not think that they are competing with our modified BEG reconstruction, but rather complementary methods in the endoscopic management of the difficult problem of post hepaticojejunostomy anastomotic stricture. That is to say, with the use of BEG reconstruction, if strictured hepaticojejunostomy follows we can use endoscopic management through the BEG gastrojejunostomy loop or through single balloon enteroscopy for management, especially that failure of balloon enteroscopy access was reported to reach 27% (ref 14).

- We agree with the reviewer that the diameter of bile duct above the stricture is an important factor in the rate of restricture after reconstruction. In our series, this diameter ranged from 6 mm to 20 mm. However, it is nearly impossible to totally prevent post hepaticojejunostomy anastomotic stricture. We added a sentence in the second paragraph of the "discussion" section about this information.

- Regarding the rate of anastomotic stricture after hepaticojejunostomy, it ranges in the literature from 2 to 25 %, which is a sizable percentage. Considering the severity of this complication and the possibility of biliary hepatic cirrhosis to follow, the management of such a complication needs to be well addressed. We think that the modification of the standard hepaticojejunostomy into BEG reconstruction could be of great help to manage biliary restenosis, if it occurs, with minimally invasive endoscopic procedure. Even if it is routinely performed, we do think that this BEG modification, especially type III, is simple and does not add any surgical difficulty to the standard Roux-en-Y hepaticojejunostomy technique.
Regarding the patient with restenosis in our series, the reviewer prefers a single balloon enterostomy. We think that the use of BEG reconstruction in this patient strengthen the chance to manage this patient by minimally invasive endoscopic procedure either by using the BEG enterogastrostomy loop or by using single balloon enterostomy, especially if either one of these two methods failed; a possibility that could actually happen.

The spelling was rechecked and corrected.

Finally we would like to thank the respected reviewer for his important remarks that enabled us to make the article more beneficial.
Reviewer number 4: Dr. Norman O Machado:

We would like to thank the reviewer for his interesting remarks and for stating that "the article is of importance in its field."

1. We modified the sentence of the aim in the "background" section of the abstract to enlighten the aim in a better expression.

2. We thank the reviewer for his opinion about the methods (appropriate and well defined).

3. We thank the reviewer for his statement about the data, the pictures and the illustrations.

4. We thank the reviewer for his statement about the manuscript.

5. We thank the reviewer for his statement about the discussion. Regarding the follow up time, we agree with the reviewer that long term complications may need longer follow up to appear. That is why we added a sentence in the fifth paragraph of the "discussion" section to comment about the follow up period.

6. Regarding the comparison between the different BEG types, we added a sentence describing these data in the conclusion section of the "abstract" and also in the conclusion section of the article manuscript.

Finally we would like to thank the respected reviewer for his valuable remarks that helped us to make the article, hopefully, more beneficial.

With best regards.

Yours sincerely

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