September 25th, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: MS-G-050240253.doc).

Title: Hyperamylasemia is associated with increased intestinal permeability in patients undergoing diagnostic oral double-balloon enteroscopy

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4990

Reviewer 1

This is an interesting paper, but some comments are important.

Response: We thank the Reviewer for his comment.

1. The sample is to small

Response: We agree that our sample size was quite small, but we discussed the influence of a small sample size in the Discussion. In order to exclude any possible influence on the results, patients with any comorbidity or disease that could affect the results were excluded, and we also excluded all patients undergoing therapeutic DBE. We could have used subgroups, but it required a too large sample size, because each disease would have been a separate group. In our study, some cases were excluded because of gastrointestinal decompression, active gastrointestinal bleeding, refusal to participate, etc. Therefore, 60 patients were recruited and received lactulose/mannitol solution, but during DBE, we had to exclude 40 patients with any comorbidity or disease to minimize the influence on PI. Hence the small sample size. Nevertheless, we observed significant associations.

2. What lesions were detected in those 20 patients?

Response: Patients were excluded if any lesion was observed. Therefore, the 20 remaining patients had no lesion.

3. When the authors say "improved DBE maneuvers is required", what do they mean?

Response: We meant more gentle insertion techniques, shortening the balloon time and reducing the number of passes. This was clarified in our revised version.

4. The introduction and discussion are too long

Response: We thank the Reviewer for his suggestion. The Introduction and Discussion were edited.

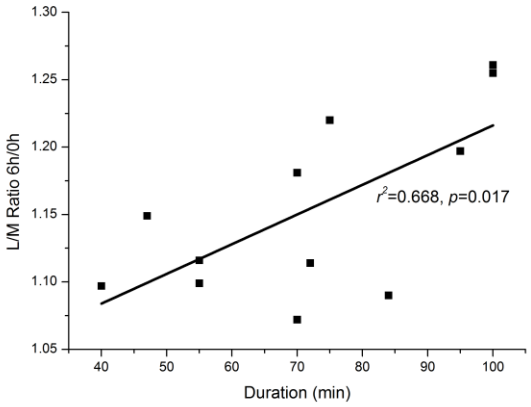
Reviewer 2

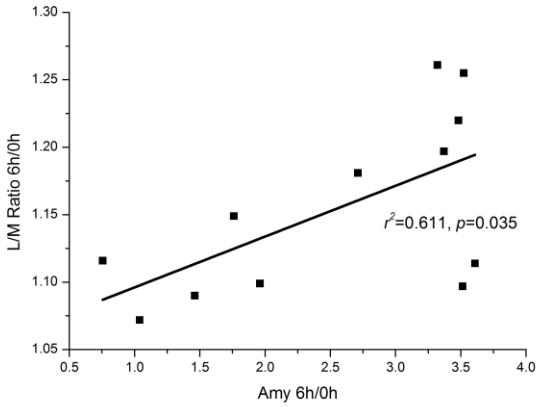
This is an interesting to address hyperamylasemia, one of the important complication after DBE. They have afddressed scientific approach to clarify the machanism. Overall messages are cleary stated.

Response: We thank the Reviewer for his comments.

In page 11, they stated that increased post-procedure IP correlated with increased serum amylase and procedure duration. Please show graph showing correlation between these parameters.

Response: We thank the Reviewer for his suggestion. This Figure was added to our revised manuscript.





in page 14, they stated that "improved DBE maneuvers is required". They should refer to this point more in detail, including how to improve this.

Response: We meant more gentle insertion techniques, shortening the balloon time and reducing the number of passes. This was clarified in our revised version.

They finally assessd 20 patients including 12 oral and 8 anal DBE. Of 20 cases,how many positive findings are found? Also how many theraputic approach was done? Is there any difference between subgroups (e.g. positive findings VS negative findings, theraputic vs non- theraputic)? Please clarify.

Response: We agree that our sample size was quite small, but we discussed the influence of a small sample size in the Discussion. In order to exclude any possible influence on the results, patients with any comorbidity or disease that could affect the results were excluded, and we also excluded all patients undergoing therapeutic DBE. We could have used subgroups, but it required a too large sample size, because each disease would have been a separate group. In our study, some cases were excluded because of gastrointestinal decompression, active gastrointestinal bleeding, refusal to participate, etc. Therefore, 60 patients were recruited and received lactulose/mannitol solution, but during DBE, we had to exclude 40 patients with any comorbidity or disease to minimize the influence on PI. Hence the small sample size. Nevertheless, we observed significant associations.

Please clarify the method that they have evaluated the insertion length.

Response: When the enteroscope reached its deepest level, we pulled the endoscope, and the insertion length was calculated as: [reference point on the endoscope - (60cm(oral) or 65cm(anal))]*8. This was added in the Methods.

Reviewer 3

This is a significant study which focused on the correlations between serum amylase level, intestinal permeability (IP), and DBE. Though DBE-associated acute pancreatitis is rare, hyperamylasemia is common but its mechanism remains unknown. This is the first study to prove the hyperamylasemia was due to enhanced IP rather than the injury to pancreas. This kind of studies are encouraged because their results will improve the clinic DBE procedure.

Response: We thank the Reviewer for his comments.

1.The sample size is small as not so powerful to make a conclusion. I do not know why the researcheres excluded enterostenosis, tumors, or inflammatory bowel disease. Even the bowel diseases will affect the results of PI, they can make a subgroup analysis. Because above diseases were the most reason to perform DBE.

Response: We agree that our sample size was quite small, but we discussed the influence of a small sample size in the Discussion. In order to exclude any possible influence on the results, patients with any comorbidity or disease that could affect the results were excluded, and we also excluded all patients undergoing therapeutic DBE. We could have used subgroups, but it required a too large sample size, because each disease would have been a separate group. In our study, some cases were excluded because of gastrointestinal decompression, active gastrointestinal bleeding, refusal to participate, etc. Therefore, 60 patients were recruited and received lactulose/mannitol solution, but during DBE, we had to exclude 40 patients with any comorbidity or disease to minimize the influence on PI. Hence the small sample size. Nevertheless, we observed significant associations.

2.If there were only 20 cases included, please don't say "A prospective study was conducted of 60 consecutive DBE patients..." in the method section of the abstract, that will mislead readers.

Response: This was edited.

3.For table 2, there is no comparison between oral and anal for PI at 0 or 6h.

Response: We agree with the Reviewer. The ratios were added to Table 2 and compared.

4.Please explain the insert length method briefly.

Response: When the enteroscope reached its deepest level, we pulled the endoscope, and the insertion length was calculated as: [reference point on the endoscope - (60cm(oral) or 65cm(anal))]*8. This was added in the Methods.

5.The introduction and discussion are too long which needs compression.

Response: We thank the Reviewer for his suggestion. The Introduction and Discussion were edited.