Response to REVIEWERS

October 1, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4755- Review.doc).

Title: Conservative treatment of early postoperative small bowel obstruction with obliterative peritonitis: 3 years follow-up

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

For reviewer 1:

The clinical study investigates the benefit of somatostatin and dexamethasone treatment in early postoperative small bowel obstruction with obliterative peritonitis. Comments: Patient's long time follow-up is evaluated with a 4-point scale. The criteria to categorize each point should be further characterized. Abbreviations are not in line. EPiSBO and EPSBO, where are the differences?

Answer:

1) Patient satisfaction was based on the core symptoms of Gastrointestinal Quality of Life Index (GIQLI) as abdominal pain, feeling of abdominal distension, flatus and stool

frequency, anorexia, fatigue, and nausea and vomiting. . The definition of “very satisfied” was no abovementioned gastrointestinal symptom in the last year, “satisfied” with occasional gastrointestinal symptoms, “unsatisfied” with several episodes of abdominal symptoms in the last year, and “very unsatisfied” with frequent abdominal symptoms.We added the classification in the Method part of the revised manuscript.

2) In the manuscript, EPiSBO means EPSBO with obliterative peritonitis, which is one subtype of EPSBO. To eliminate the possible misunderstanding, we use the abbreviation ESPBO-OP (EPSBO-obliterative peritonitis) instead of EPiSBO in the revised manuscript.

For reviewer 2:

1. This article is a prospective study, but there is no mention of an end point of the study. Please state primary and secondary end point of the study in the method section. 2. Even though the patients enrolled in this study were unable to be definitively diagnosed with EPiSBO through surgery, the authors should show the differential diagnosis in the methods/patients section between EPiSBO and other small bowel obstructive diseases, which have similar clinical manifestations on patient’s clinical presentation, physical examination findings, and medical history and findings of plain film and CT, such as intestinal pseudo-obstruction, partial mechanical bowel obstruction, paralytic ileus after abdominal surgery, mesenteric ischemia. I recommend the authors state how they were able to make a differential diagnosis on the basis of only these clinical parameters. 3. The authors stated that the patients with mechanical bowel obstruction, paralytic ileus, or idiopathic pseudo-obstruction were excluded in this study, but patients suffering from EPiSBO most definitely have partial mechanical bowel obstruction. Please elaborate on this. 4, The authors frequently went back and forth using their abbreviations, such as postoperative small bowel obstruction with obliterative peritonitis (EPiSBO), somatostatin (SS) and dexamethasone (DM).

Answer:

1. The early primary endpoint is time to resolution of bowel obstruction and length of hospital stay, while the secondary endpoint is the daily NG output and NG duration, treatment related complications, postoperative obstruction relapse, and patients’

satisfaction. The endpoints of the study were stated in the method section.

2. Differential diagnosis of EPSBO-OP from other small bowel obstructive diseases is sometimes quite difficult. As conservative treatment is the standard therapy for EPSBO-OP, we can only differentiate it from other type of SBO from clinical parameters. As for intestinal pseudo-obstruction partial mechanical bowel obstruction, paralytic ileus after abdominal surgery, they generally presented with dilated bowel loop and air-fluid levels in the X-ray film or a transition zone in CT scan, which is absent in the current series, as shown in Figure 2. For acute mesenteric ischemia, the common presentation in CT-scan is bowel wall thickening; however, patients often have concomitant symptoms or signs such as high fever, persistent leukocytosis, severe colicky pain, bloody diarrhea, which will not respond to conservative therapy and often worsens during treatment. To guarantee a homogenous patient population, we excluded patients with suspicion for these diseases on entry (as shown in the revised manuscript in the Exclusion criteria part), and also we kept close observation of the patients during treatment and excluded patients with misdiagnosis on entry. For example, four patients in the control group was found eventually to have mechanical obstruction and intestinal fistula during treatment and excluded for analysis.

3. EPSBO-OP may have a combination of mechanical obstruction and diffuse small bowel and colonic ileus, this has also been mentioned in ACS SURGERY: ACS Surgery: Principles & Practice, 2007 Edition. Section 5, Chapter 4: INTESTINAL OBSTRUCTION. We added this in the Introduction part of the revised manuscript.

4. Sorry for the inconvenience, we have standardized the abbreviations in the revised manuscript.

For reviewer 3:

This is a randomized trial of standard therapy (TPN and NG suction) and somatostatin and dexamethasone given for one week compared with standard therapy alone for the treatment of early postoperative small bowel obstruction (EPSBO). The study took place at a single center and included 70 patients randomized between 2002 and 2009. Major findings: treatment with somatostatin and dexamethasone resulted in reduced NG output, shorter duration of NG tube use, earlier recovery of bowel function, and shorter length of

stay, without increase in complications. Specific comments: 1. The abstract and introduction should be revised to make clear what the aim of the study is. For example, the aim of the study was not to evaluate conservative therapy as stated. The aim was to evaluate the effects of somatostatin and dexamethasone in addition to standard therapy for promoting the resolution and symptom control of EPSBO. Again in the conclusion in the abstract and at the end of the discussion, it should state: "Treatment with SS and DM in EPSBO with obliterative peritonitis reduces the time to resolution of obstruction as well as the length of hospital stay without increased the relapse of obstruction compared with standard conservative therapy." In the conclusion in the last paragraph of the discussion should not refer to "conservative therapy" but to the actual treatments. 2. Methods- the section should be revised and changed to past tense throughout. Also please indicate if terminal disease or presence of metastatic cancer was an exclusion. 3. Results Table 2: please include the number of patients with abdominal malignancy in each group. 4. Results page 7: remove"NG depression" and insert "NG tube use". 5. Add to the limitations in the discussion is the fact that the study was non-blinded and the physicians were aware of what therapy each patient had. 6. Figure 3 – please increase the size of the arrowhead in the figure. 7. Table 3 footnotes: please define "postoperative satisfaction>3".

Answer:

1. The aim of the study is made clear in the abstract and conclusion part in the revised manuscript.

2. The Method section has been change to paste tense. Terminal disease and presence of metastatic cancer was excluded in the inclusion criteria.

3. The number of patients with abdominal malignancy in each group was included in Table 2

4. "NG depression" was removed and "NG tube use" was inserted.

5.The limitation that the study was non-blinded was discussed in the Discussion part.

6. The size of arrowhead in Figure 3 was inceased.

7. Patient satisfaction>=3 means that patients are very satisfied or satisfied. Patient satisfaction was based on the core symptoms of Gastrointestinal Quality of Life Index (GIQLI) as abdominal pain, feeling of abdominal distension, flatus and stool frequency, anorexia, fatigue, and nausea and vomiting. The definition of "very satisfied" was no

abovementioned gastrointestinal symptom in the last year, “satisfied” with occasional gastrointestinal symptoms, “unsatisfied” with several episodes of abdominal symptoms in the last year, and “very unsatisfied” with frequent abdominal symptoms.

3 For the comments by the editors, we have made revision in the revised manuscript.
How many days in total are these drugs given. Confusing sentence, what do you mean by quickly withdrawing. Is it reducing dose? Need clarification.
Answer: The duration of somatostatin and dexamethasone treatment is added in the Result part.

Why did you choose the outcome as passing flatus for the intervention group and NG output as the criteria for the control group. Both the groups should be decided as passing flatus or reducing NG output as the marker of success of treatment. Please elaborate on this.
Answer: We chose the criteria as passing flatus for stopping somatostatin usage, as for some patients, SS usage can eliminate the need for NGT due to its anti-secretory effects ; however, it does not mean that these patients have resolution of obstruction. If we stop SS, the patients may have a reboundance of GI secretion and will need an re-insertion of NGT. Therefore, elimination of NG tube usage did not equal to the resolution of obstruction. We used different criteria for somatostatin stoppage and NGT stoppage. The criteria of complete resolution of obstruction were defined as symptoms and signs of obstruction subsided, a return of normal flatus and defecation, and no relapse of obstructive symptoms after withdrawal of SS.

Final comments: I congratulate the authors for this difficult study well carried out and also they knew their shortcomes in their study. The number of patients were small. There was no suggestion of power calculation or blinding.
Answer: the method of power calculation was added in the Method part. Lack of blinding is the limitation of the current study, we have pointed out this in the Discussion part.

There was no mention about the tolerability / side effects of the Octreotide and

dexamethasone. Finally, I would like to see the revised paper after addressing the queries, prior to publication. Thanks

Answer: Tolerability and side effects of somatostatin and dexamethasone were Metioned in the Result part.

Mechanical obstruction and abscess/fistula must have been excluded prior to randomization. If they have developed such complications after starting treatment, they must be included in the statistics as Intention to Treat analysis. Editor can check with statistician for this.

Answer: We excluded four patients for analysis as they withdrawn from the study because they were found to not meet the inclusion criteria during treatment. Therefore, per protocol analysis (PP analysis) instead of intention to treat analysis was used in the current study. We explained this in the Result part.

Another point is that whether any power calculation was carried out or not? (Figure 1)

Answer: Power calculation was carried out, as shown in the Method part.

More detailed description of the randomization technique, any attempt to follow blinding of the intervention should be mentioned which will make this more robust paper. (Figure 1)

Answer: Assignments were based on computer-generated randomizations that were kept in sealed, sequentially numbered envelopes until used, as shown in the Method part in the revised manuscript. The current study is a non-blinded study, and this is the limitation of the current study, we have pointed it out in the discussion part.

Was there any specialist GI radiologist involved in interpreting the x-rays and CT scans. This has to be mentioned in the methods. (Figure 2)

Answer: Yes, This has been mentioned in the methods part)

If you have any questions, please feel free to contact us.

Thank you again for considering of publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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