ANSWERING REVIEWERS

October 6, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: TEXT WJG 381.doc).

Title: Can Mosapride Citrate Reduce the Volume of Lavage Solution for Colonoscopy Preparation?

Author: Masahiro Tajika; Yasumasa Niwa; Vikram Bhatia; Shinya Kondo; Tsutomu Tanaka; Nobumasa Mizuno; Kazuo Hara; Susumu Hijioka; Hiroshi Imaoka; Koji Komori; and Kenji Yamao

Name of Journal: *World Journal of Gastroenterology*

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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

We would like to thank the reviewers for their constructive comments. We have tried to include the suggestions of the reviewers in the revised manuscript, and would like to give a point-by-point reply to their comments.

(1) Reviewer No.00033045

MAJOR COMMENTS/REVISION

Bowel prep scale: As you mentioned, Ottawa bowel prep scale or Boston bowel prep scale were

appropriate for bowel preparation assessment in our study. The reason why we selected the Aronchick scale was that in cases in which additional bowel preparation was needed, such cases could be defined as 'inadequate'. However, the Aronchick scale was designed to assess bowel preparation of the entire colon. It's our mistake. So, I added sentences in the limitation (page 17, para17).

Results: As you mentioned, an interpretation of our results seemd to be wrong. It seemed to be difficult to demonstrate the non-inferiority of 1.5 L PEG with mosapride from our results. So, I changed the conclusion and discussion (page 4, para 7; page 15, para 3; page 18, para 4).

Study Design: As you mentioned this study was designed as a non-inferiority trial with a very small difference in bowel preps. So, I mentioned it in the limitation (page 17, para).

MINOR COMMENTS/REVISION

- According to your suggestion, I deleted these sentences and changed references.

Patients and Methods – First 2 sentences

- Discussion – Paragraph 2
- Discussion – Paragraph 3 – All except 1st sentence
- Please adjust all hyphens between page numbers in references to be consistent throughout.

(2) Reviewer No.00035894

I red with interest the study suggesting that bowel cleansing with 1.5L of PEG solution with a prokinetic agent (mosapride citrate) is not inferior to bowel cleansing with 2.0L of PEG with mosapride citrate.However, the study design is confusing as well as the interpretation of the results. I have doubts if the conclusion is supported by data.

Thank you very much for your proper comments. As you mentioned, an interpretation of our results seemd to be wrong. It seemed to be difficult to demonstrate the non-inferiority of 1.5 L PEG with mosapride from our results. So, I changed the conclusion and discussion (page 4, para 7; page 15, para 3; page 18, para 4).

The major shortcoming of the present study is its design. There should have been a third group – PEG 1.5L + placebo. How the authors explain better results of bowel cleansing in the present study (above 80% of optimal preparations) with 1.5 L of PEG + mosapride while in the previous study, the

rate of optimal bowel cleansing were bellow 80% with 2.0L of PEG with mosapride and even bellow 70% with PEG 2.0L. How the authors explain that mosapride accounts for more than 20% of improvement in bowel cleansing?

As you mentioned that the optimal preparation rate (OPR) of 2.0L of PEG with mosapride in previous study was lower than 1.5 L of PEG with mosapride in present study. Indeed, it was strange. However, these two studies were performed separately. So, there would be differences in season, investigator, or practice of investigators, that might make the difference in two studies. As you mentioned, there should have been a third group – PEG 1.5L + placebo. Although you mentioned that mosapride accounts for more than 20% of improvement in bowel cleansing, to the utmost 15% from our results in previous study.

The current design, unfortunately, cannot answer an important question whether 1.5L of PEG could also have been adequate? In view of different percentage of patients with optimal preparation among studies, I think the third group of patients should have been included. This must be, at least, discussed.

As you mentioned, an interpretation of our results seemd to be wrong. I seemed to be difficult to demonstrate the non-inferiority of 1.5 L PEG with mosapride. So, I changed the conclusion and discussion (page 4, para 7; page 14, para 1; page 15, para 3; page 18, para 4).

How the authors explain that in a majority of other studies prokinetics did not significantly improve the quality of bowel cleansing.

According to your suggestion, I added the sentence in the discussion (page 15, para11).

I wonder whether this clinical trial was registered and whether patients signed informed written consent. Those are very important points.

Of course, this clinical trial was registered and patients signed informed written consent. I added the sentence in the methods (page 7, para2).

The conclusion of authors (abstract) is different from statements done by the authors in the discussion (page 16, 1st paragraph). The authors say that "15 mg of mosapride may be insufficient to compensate for reduction of 0.5 L of PEG..." while the conclusion of authors is that "1.5 L of PEG

+ mosapride is not inferior to 2.0 L of PEG + mosapride". It is not really clear what is the main conclusion.

As you mentioned, an interpretation of our results seemd to be uncler. So, I changed the conclusion and discussion (page 4, para 7; page 15, para 3; page 18, para 4).

The authors propose more additional studies investigating different aspect of optimal dosing of mosapride should be done. I believe that less studies, however with a high quality design, is a better strategy. Why not to perform a study with Latin square design (different doses of mosapride and different doses of PEG).

Thank you very much for your precise advice.

Page 4: In western countries, not 4L but 3-4 L of PEG is recommended

According to your suggestion, I changed it.

The method section is quite long and not all details are necessary to address.

According to your suggestion, I deleted and changed them as possible I can.

Results: Why the authors do not start with showing results concerning the main endpoint? I would suggest, just after baseline characteristics, to continue with results concerning the main endpoint.

According to your suggestion, I changed them. (page 11, para 20)

The method and results sections are too long, on the other hand, the discussion does not address several important issues (why other studies with prokinetics did have not shown benefit, the issue of adverse events of adding a prokinetics agent to a PEG solution, some patofysiological aspects etc.).

According to your suggestion, I changed them as possible I can.

Page 15, 1st para, 5 and 6th line- what the authors mean that "mosapride significantly improved small bowel transit time ....in pts with IBS? How the improvement was defined?

I deleted the reference because of an inappropriate expression.

The first paragraph on page 16 is not clear and should be reformulated.

According to your suggestion, I changed them (page 16, para 22).

Table 1: The sum of patients in the 1.5 group (eg male + female) is 122 and not 126. Why ?

It was my mistake. I changed it. Thank you.

Table 2: Time to first defecation – units are missing

It was my mistake. I changed it. Thank you.

How the authors explain (should be discussed) that time to preparation was not different between the groups. Did patients drink 2L of PEG as quickly as 1.5L of PEG? What was the time of preparation itself?

Although there was no significant difference between both groups, 18 patients required additional preparation in the 1.5 L group compared with 11 patients in the 2 L group. One of the reason why the time to preparation were similar in both groups. I added these sentence in discussion (page 15, para1).

Feel of peristalsis (page 28) – should be explained what does it really mean

It means that difficulty in observing the lumen of the colo·rectum because of peristalsis, because it is said that mosapride encourage peristalsis(page 10, para11).

A higher number of patients in 1.5 L group had inadequate preparation (14 vs. 21). Even if not significant, the authors should comment on clinical relevance of this finding.

According to your suggestion, I added a sentence (page 14, para 23).

Table 3: Overal score – "n" and "%" should be shown but only numbers are displayed.

It was my mistake. I changed it. Thank you.

I feel there are too many tables and images and seem quite busy. I do not think it is necessary to show all details, especially of those results showed in the manuscript. The numbers do not need to be repeated.

According to your suggestion, I deleted and changed them as possible I can

Finally, 48 references are inadequate for an original paper, I feel this number should be decreased.
According to your suggestion, I changed and deleted them as possible I can.

In summary, the manuscript needs a major (if any) revision. The text should be clarified, shortened, the discussion must be improved, the tables and images must be redone. The authors should rethink the idea of "less studies with better design", or at least discuss the problem with a current design. Also, the minor points should be addressed.
I mentioned above.

(3) Reviewer No.00033377

Comment on patient selection.
-According to the study population, the authors do not explain why patients between the ages of 20-80 underwent the colonoscopies. Were these screening or diagnostic? I assume these were colonoscopies for all indications and not just screening but this is not clear. If colonoscopies were not just for screening, how many were screening and how many were diagnostic in each arm?
According to your suggestion, I showed the number of indication and added the sentence (page 7, para12 and Table 1).

Comments of bowel preparation scale.
-The authors of the study used a modified Aronchick's criteria to assess the efficacy of the bowel preparation. I believe that this may be one of the studies major weaknesses, since it is questionable—at best—if Aronchick's is actually a validated scale with only one abstract published in AJG 1999 (#360). Additionally, the authors modified this scale to independently grade the right and left side of the colon, when the scale was constructed to grade the overall prep of the colon. -A better scale that could have been used is the Ottawa scale but nevertheless the authors went through a callibration exercise. This should be mentioned as a limitation.

As you mentioned, Ottawa bowel prep scale or Boston bowel prep scale were appropriate for bowel preparation assessment in our study. The reason why we selected the Aronchick scale

was that in cases in which additional bowel preparation was needed, such cases could be defined as 'inadequate'. However, the Aronchick scale was designed to assess bowel preparation of the entire colon. It's our mistake. So, I added sentences in the limitation (page 17, para17).

Comment on evaluation bowel preparation.

-The authors note that "after colonoscopy, two observers including the operator decided the score by mutual agreement". However, there is no mention as to who the second observer is. Is it another operator, a fellow or a nurse? Was the second observer in the procedure room?

According to your suggestion, I added the sentence (page 9, para 5).

-The authors also note the "If the decision was discordant, a second expert reviewer graded and scored the recorded images". This is a probaly a third reviewer but were these images pictures or was the entire colonoscopy recorded (video) and later viewed by the second expert reviewer?

According to your suggestion, I added the sentence (page 9, para8).

-The authors fail to mention the time that the colonoscopy took place. Were they towards the earlier of the afternoon or the later part of the afternoon? Was there an equal distribution between the afternoon procedures in regards to "early afternoon" vs. "late afternoon". This is important to know as patients who may have waited for longer periods of time are expected to have a deterioration of their prep.

I'm sorry, I forget it. So, I added the sentence (page 8, para 18). However, I mentioned it as elapsed time from last fluid intake to colonoscopy in Table 2, and no difference in both group.

Comment on discussion.

-The authors state in the introductory paragraph that 1.5L PEG-electrolyte plus mosapride was a non-inferior preparation, especially for the right side of the colon compared to the 2L PEG-electrolyte plus mosapride. This is again restated on page 12, second sentence of paragraph two. This statement is probably based on a lesser difference in optimal prep in the right as opposed to the left. However, as referenced to in table 3, there is a p value of 0.006 with a higher group of patients having a fair prep in the 1.5L group. Therefore, the optimal prep difference is

skewed by the 1.5L group having a larger amount of patients falling in the fair category and less patients in good or excellent.

As you mentioned, interpretation of our results seemd to be wrong. I seemed to be difficult to demonstrate the non-inferiority of 1.5 L PEG with mosapride. So, I changed the conclusion and discussion (page 4, para 7; page 15, para 3; page 18, para 4).

-The authors also defined optimal preparation as excellent, good and fair. I feel that the word "optimal" should be substituted for "adequate".

As your suggestion, the word "optimal" seems to be substituted for "adequate". I changed it. Thank you very much.

3 References and typesetting were corrected

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

Sincerely yours,

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