Format for ANSWERING REVIEWERS

September 24, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13075-review.doc).

Title: Electrolytes changes after bowel preparation for colonoscopy: A randomized controlled multicenter trial

Author: *Kyong Joo Lee, Hong Jun Park, Hyun-Soo Kim, Kwang Ho Baik, Yeon Soo Kim, Sung Chul Park, Hyun Il Seo*

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13075

We would like to thank you and the referees of World Journal of Gastroenterology, for taking the time and effort to review our manuscript. Many of the valuable and constructive points that the referees pointed out, were well taken by all the authors. After going over the referee's comments, we made revisions and changes made in the manuscript in hopes of improving our paper.

We hope that our revisions meet the referees' comments. We believe that the comments have significantly improved the quality of our manuscript and hope you will find our revised manuscript acceptable for publication.

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

Sincerely yours,

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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

Reviewed by 00504462

(1) Were all the adverse effects benign?

Response : There were no serious adverse events due to electrolyte imbalance such as neurologic symptoms or mental change. Therefore, all the adverse events were benign and easily controlled.

(2) 100% of all the included patients had a complete and successful preparation. What was the indication for the procedure?

Response : Thank you for the reviewer's point. The indications of the procedure were colon cancer screening and functional gastrointestinal symptoms. We added the indications to 'Patients and Methods' and 'Table 1'.

(3) In how many patients you reached the cecum or the terminal ileum? Was it 100%?

Response : In our study, we tried to reach the terminal ileum and cecum in all patients. But, we failed to reach cecum base in three patients. However, we could reach up to proximal ascending colon and were able to evaluate bowel preparation.

(4) Can you tell us about your adenoma finding rate? Can you mention the median time of the duration of the procedures in each group?

Response : Because we focused on bowel preparation and electrolyte changes in the study from the beginning, unfortunately, we could not evaluate the number of adenoma and median time of the procedure. We have added the point as a limitation of the study in the revised manuscript.

(5) Is the PEG-Asc composition, pH and taste equal or equivalent as the one that is marketed in other countries?

Response : All the properties are equivalent to the one that are in marketed in other countries.

(6) Did you receive any sponsorship from the PEG-Asc manufacturer?

Response : As we mentioned in cover page, Taejun Pharmaceutical Company provided both PEG-Asc and 4-L PEG for the study.

Reviewed by 00071725

(7) How the patients were randomized?

Response : Thank you for your valuable point. We used a computer generated randomization table sealed in opaque envelopes and assigned to PEG-Asc group or 4-L PEG group. This study was performed as an operator blind process. We added the sentence in 'Method' part.

(8) What are the primary and secondary outcome measures?

Response : Thank you for your valuable point. The primary outcome was electrolyte imbalance. The secondary outcomes were efficacy for bowel preparation and patient compliance. However, the sample size was based on bowel preparation rate, because most previous study evaluating electrolyte

imbalance was set by the bowel preparation as well and it was difficult to calculate the sample size based on several kinds of electrolytes.

(9) How the sample size was calculated?

Response : As we mentioned in response 8, we calculated the sample size based on the difference of bowel preparation although the primary endpoint was electrolyte imbalance, because there was difficulty and limitation to calculate the sample size based on electrolytes.

We consulted to the department of statistics.
We assumed appropriate bowel preparation as 75% of the patients in 4-L PEG group. We defined as statistically non-inferior when the difference was less than 20% between PEG-Asc and 4-L PEG. Alpha is the probability of rejecting a true null hypothesis. Alpha was 0.05. Beta is the probability of accepting a false null hypothesis. Beta was 0.8. The drop-out rate was 5 percent.
In this case, total 240 patients were needed (PEG-Asc 120 patients, 4-L PEG 120 patients).

We have added the sample size in 'Patients and Methods' part.

References

Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.
Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

Reviewed by 00188264

(10) Patients allocation and allocation concealment was not mentioned, the same as the process of blinding.

Response : We randomly assigned patients to PEG-Asc or 4-L PEG using a computer generated randomization table sealed in opaque envelopes. Also the endoscopists were blinded to the type of solution used. We added the sentence to 'Patients and Methods' part.

(11) Sample size calculation was not provided, not sure how did they come up with the number provided and based on what outcome

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Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

(12) Exclusion of patients with renal and heart failure limit generalizability

Response : We agree with the reviewer's comment. This is one of the limitation of our study. Patients with renal or heart failure may be influenced by electrolyte changes and there were safety concerns. As this study was to compare the safety on electrolyte balance, we excluded those patients with high risk. A large-scale and well-designed study is needed to ensure whether PEG-Asc is safe in patients with this medical condition. We added the reason in 'Discussion' part.

(13) Why patients in the conventional 4L of PEG received 3L of PEG the night before and 1L the morning of the procedure instead of 2L the night before and 2L the morning of the procedure? That might decrease the efficacy of 4L PEG

Response : Thank you for the reviewer's comment that we have not recognized. Patients felt difficulty to take additional 2L in the early morning. Therefore, in our institute, patients has been recommended to take 2.5 to 3L of PEG the night before the exam, and 1-1.5L in the morning of the examination. Also we presumed initial higher intake of 3L may be beneficial to push out the solid stool first, we have let the subjects to take 3+1L split dose, which has been reported to be superior to that of single-dose. Corporaal S. and Park SS. reported 3+1L split dose were superior to single-dose bowel preparation.

Reference

Corporaal S, Kleibeuker JH, Koornstra JJ. Low-volume PEG plus ascorbic acid versus high-volume PEG as bowel preparation for colonoscopy. Scand J Gastroenterol. 2010 Nov;45(11):1380-6.

Park SS, Sinn DH, Kim YH et al. Efficacy and tolerability of split-dose magnesium citrate: low-volume (2 liters) polyethylene glycol vs. single- or split-dose polyethylene glycol bowel preparation for morning colonoscopy. Am J Gastroenterol. 2010 Jun;105(6):1319-26.

(14) Authors didn't explain the changes noticed in electrolytes disturbance and the discrepancy between their findings and previous studies

Response : The authors are grateful to the reviewer's valuable point, the crux of our study. We have described the different findings with previous study as following; However, there were few studies concerning electrolyte changes after bowel preparation. Furthermore, there was no study targeting Asian patients. As the body shape and dietary pattern are different between Asian and Westerners, there would be difficulties and limitations in direct comparison of ours with previous studies. Therefore, a large study is needed to compare electrolytes changes in Asian and Westerner.

Our study showed increased serum potassium, chloride, calcium, and phosphate concentrations after bowel cleansing with PEG-Asc, which was different slightly from previous studies. However, those are usually minor and there were no electrolyte imbalances requiring urgent interventions. In particular, our study showed that increased phosphorus level was more commonly observed in the PEG-Asc group than that in the 4-L PEG group. In contrast with NaP solution, PEG-Asc does not contain phosphorus components, and the rate of phosphorus increase was within the normal range, less than 10% in the group (about 50% of that seen with NaP). Therefore, there was no remarkable consequent change in serum calcium level with fatal complication such as nephrocalcinosis.

In spite of substantial changes in electrolytes, there were no constant patterns of change through a

few studies including our study. We assume that electrolyte changes after intake of PEG-Asc are transient and minor, and recovery from these changes could be easily achieved by homeostatic mechanisms. Further study is needed in patients with renal impairment whose renal homeostatic mechanisms are compromised.

We have changed the context in the revised manuscript.

(15) As authors mentioned, one of the limitation is failure to measure serum bicarbonate, I am not sure why (no reason was provided)? Especially that one of the biggest concern of ascorbic acid is acid-base disturbances

Response : Thank you for the reviewer's sharp point. At the beginning of the study, we focused only major electrolyte changes including sodium, calcium, phosphate, and serum osmolarity. Also, the measurement of vitamin C level costs high. However, we recognize that this was one of the major limitation of the study, necessitating further large study in the patients with at risk of electolyte imbalance. We changed serum bicarbonate to vitamin C concentration.

3 References and typesetting were corrected