

**March 10th, 2020**

To Prof. Subrata Ghosh  
Editor in Chief of World Journal of Gastroenterology

Dear Editor,

enclosed you find the revised version of our invited manuscript entitled **“Effectiveness of very low-volume preparation for colonoscopy: a prospective, multicenter observational study”**.

We modified the paper according to reviewer comments, and we wish to thank the editors and referees for the helpful comments, which have greatly contributed to the improvement of the manuscript. You will also find a letter itemizing the changes we have done, as point-by-point reply (in the manuscript, all sentences added to the revised version are underlined).

We hope that the paper is now acceptable for publication, and look forward to hearing from you soon.

Yours sincerely,

**Marcello Maida MD**  
Specialist in Gastroenterology  
Mail to: marcello.maida@hotmail.it  
Mobile: +39.3287136871

The original research entitled “Effectiveness of very low-volume preparation for colonoscopy: a prospective, multicenter observational study” represents a very useful manuscript for gastroenterologists and, implicitly, their patients. Its originality comes from presenting, for the first time, the results of a real-life study setting. A big bonus is the large number of patients, from five centres, enrolled prospectively. Results showed the high effectiveness and tolerability of very low-volume preparation (1-L PEG-ASC) for colonoscopy as compared with a 2-L and 4-L preparations. By using a lower-volume solution for bowel cleansing is expected that more patients will accept colonoscopy, therefore with huge health benefits, both at individual and general level, on the health care system costs, since early detection is always better. In the whole manuscript, the authors paid much attention to details, which is much appreciated. Title and Key abstract are well chosen. Abstract, Core tip and Introduction contain accurate data, easily to be followed and understood.

Minor comments/suggestions:

1. Introduction:

- a. Please define NER 1006 (as” 1L polyethylene glycol plus ascorbate”), before using the abbreviation.

ANSWER: “NER1006” has been replaced with 1L PEG-ASC both in the abstract and in the text, therefore it don’t need to be defined.

- b. Please decide whether you use NER1006 or PEG-ASC (the latter being more used in your manuscript), in order to avoid confusion for readers.

ANSWER: According to reviewer suggestions “NER1006” has been replaced with 1L PEG-ASC both in the abstract and in the text.

2. Methods: well explained. Suggestion – please write separate paragraphs for design, patients inclusion and exclusion criteria), techniques and statistics.

ANSWER: We thank the reviewer for this suggestion. The following separate paragraphs have been included in the Methods section: Study design and participants, Techniques, Outcomes and measurement, Statistics and Ethics.

3. Results: Both text and tables & figures are clearly presented and of good quality.

- a. Tables 1, 2 and 3: Please explain (under the table) the abbreviations PEG-ELS and PEG-ASC.

ANSWER: Abbreviations of PEG-ELS and PEG-ASC has been explained under every table, as suggested.

- b. After the sentences “With regard to the preparation regimen, 62.5% of patients performed an afternoon-only and 37.5% an afternoon-morning (split) preparation. The mean time between the assumption of the last dose and the beginning of the colonoscopy was  $11.9 \pm 2.8$  and  $4.9 \pm 1.8$  hours in the two groups, respectively.”, please mention how many in each of the three groups. This could be of paramount importance when interpreting the results. This particular instance is not mentioned in Table 1.

ANSWER: We thank the reviewer for suggestion. The preparation modality (afternoon only vs split) was similarly distributed among the three groups. This was added in the text as suggested.

Moreover, we added the number of patients undergoing afternoon only and split preparation also in Figure 1 for a better comprehension.

Moreover, since preparation modality may represent a confounder, we included this variable in the multivariate model. Results from multivariate analysis are therefore controlled for preparation modality, that allows a correct interpretation of the results.

- c. Later on, in the results, the authors wrote “When assessed by preparation modality, cleansing success was 68.1%, 65.6% and 83.3% (p=0.065 for 1L vs. 2L; p= 0.069 for 1L vs. 4L) for afternoon-only preparation and 90.3%, 88.3% and 91.9% (p=0.84 for 1L vs. 2L; p=0.84 for 1L vs. 4L) for split preparation in the three groups, respectively”. Therefore, there was no significant difference between the 3 regimens. This should be highlighted.

- d. Results also showed that cleansing success was significantly better only with the 1-L vs the 2-L, in the afternoon-morning regimen. No other significant differences were found, even with the 4-L subgroup. No difference at all in the afternoon-only preparation.

ANSWER (points c & d): Cleansing success, as well as High-quality cleansing of the right colon were significantly higher for 1L PEG compared to 2 and 4 L solutions overall. This superiority tends to disappear when the same outcomes are analysed by method preparation modality (afternoon-only vs afternoon-morning). This has already been underlined in the discussion when we state that “This effect is probably secondary to the effectiveness of a split modality, widely shown by several lines of evidence, which may smooth out the differences of efficacy between the three solutions”. Moreover, despite the absence of significant difference between the two regimens in the crude analysis, Plenvu was confirmed to be an independent predictor of overall success over the 2L-PEG preparation and, marginally, over the 4L-PEG solution and of and high-quality cleansing of the right colon both over the 2L and the 4L-PEG solution.

This association is independent from the preparation modality, since considering the importance of preparation modality as confounder, multivariate model has been properly controlled for this variable.

The cleansing success rates are overall low. How do the authors explain these results?

ANSWER: We agree that the cleansing success rates are suboptimal. This may depend on the presence of a relevant proportion of elderly, inpatients and patients with comorbidities, which reduces the probability of cleansing quality. This point has been included in the discussion.

- e. Figures 1 (a to e), 2 and 3: Please explain the abbreviations PEG-ELS and PEG-ASC.

ANSWER: Abbreviations of PEG-ELS and PEG-ASC has been explained under every figure, as suggested.

- f. Paragraph “Predictors of cleansing success and high-quality cleansing of the right colon”:

f1. First sentence – “The logistic multiple regression model” – please insert “for overall cleansing success”.

ANSWER: The sentence has been corrected as suggested.

f2. Next sentence: “The logistic multiple regression model” – please insert “for high-quality cleansing of the right colon.

ANSWER: The sentence has been corrected as suggested.

- g. Paragraph “Adherence and tolerability” – There was no significant difference between the 3 subgroups; therefore writing that “Adherence was also higher in the group of patients assuming the 1L-PEG” is not correct.

ANSWER: We thank the reviewer for suggestion. We modified the sentence as follows: Our study also showed higher adherence to preparation with Plenvu, compared with other groups, even if this superiority was only marginally significant only over the 4L-PEG and not significant over the 2L-PEG.

We also removed the sentence “Adherence was also higher in the group of patients assuming the 1L-PEG”

- h. Tolerability – “Figure 3 b” should be inserted in the text after the sentence “tolerability was higher for the 1L preparation compared to the 2 and 4L-PEG solutions, with an average score of  $7.9 \pm 1.3$  vs.  $7.1 \pm 2.0$  and  $7.3 \pm 1.9$  ( $p < 0.001$  for 1L vs. 2L;  $p < 0.001$  for 1L vs. 4L)” and deleted from where the authors mentioned it, as it is not correct.

ANSWER: We thank the reviewer for suggestion. The Figure 3b has been cited, as suggested, in its right place.

-i. Supplementary Table 1 and text regarding Safety: How do the authors interpret the highest incidence of vomiting in the 1-L preparation group? It is too briefly mentioned in Discussion. But, vomiting should affect tolerability. Therefore?

ANSWER: We thank the reviewer for suggestion. As reported in the discussion the higher incidence of vomiting after the consumption of Plenvu is probably secondary to the greater amount of ascorbate, which is present in the second dose. Unfortunately, data from this study do not allow to provide further speculation. Even if vomit may affect the tolerability, tolerability is an average effect that depends on several factors. In our study, Moreover “it is crucial to remark that, the intensity of vomit was mild and not able to compromise the tolerability of bowel preparation. As a matter of fact, in our study, Plenvu was the most tolerated solution and it was also found to be an independent predictor of tolerability”. We added this sentence in the discussion paragraph to better argument this point.

- j. Supplementary Table 1. Please write the abbreviations TEAEs, PEG-ASC and PEG-ELS under the table.

ANSWER: Abbreviations has been added under the table, as suggested.

4. Discussion: a. What do the authors mean by “In attrition, the combination of 1L-PEG solution and of a split regimen..”? Does not make any sense!

ANSWER: The sentence was incorrect and has been amended as follows: “In particular, the combination of 1L-PEG solution and of a split regimen showed to provide the highest tolerability”.

b. Strength and limitations of the study were well presented in the Discussion.

ANSWER: We thank the reviewer for the evaluation.

5. Format of the style requested by the journal, including references is not adequate.

ANSWER: Format of the text, in particular references format, has been modified.