

Response to reviewers

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 35918

Manuscript Type: Randomized Controlled Trial

Title: A Multicenter, Randomized Study to Optimize Bowel Preparation for Colon Capsule Endoscopy

Authors: David Kastenber, Wilmot C Burch Jr., David P Romeo, Pankaj K Kashyap, David C Pound, Neophytos Papageorgiou, Ignacio Fernandez-Urien Sainz, Carly E Sokach and Douglas K Rex

Dear editors,

Thank you for the opportunity to revise our manuscript in your journal. Please find our comments to the editors addressing each requested item.

Answer: All authors have signed the copyright assignment form, titled "35918-Copyright Assignment Form".

Reviewer #1 Comments to the Authors: Dear Editor Although the study is terminated earlier and did not reach the calculated sample size I can recommend the paper for publication due to ongoing debate regarding the bowel preparation and procedure regimen during the examination. I have some minor comments: • The title is no related to the topic- the title is regarding the bowel preparation but the aim of the study is: "This study evaluated the efficacy and safety of a new CCE preparation regimen that combines low dose OSS with diatrizoate solution as a boost agent ". Boost and bowel preparation is not the same to me. Booth groups received the same cleansing regimen and the differ just in booster medication • Please use SI measures instead of imperial

Answer:

- Title of the manuscript: Traditional methods of complete colon evaluation with colonoscopy, barium enema, or CT colonoscopy necessitates bowel preparation entirely before the study begins. Capsule colon shares this, but also incorporates

intra-procedure “boosts” providing both capsule propulsion and additional bowel cleansing. We believe it most ideal to consider the entire preparation process (pre- and intra-procedure) to be “bowel preparation” for capsule colonoscopy and therefore prefer to leave the title intact.

- Please use SI measures instead of imperial: As some readers of this journal reside in countries that use SI measures and other countries that use imperial measures, we would prefer to use both in the text of the manuscript so the volumes are clear to all readers. **We have made these changes so readers have both available throughout. (Carly.... The “royal” we)**

Reviewer #2 Comments to the Authors: I have read with great interest this MCT based on the evaluation of colon cleansing with two bowel regimens: double vs simple osmotic agents. The authors have demonstrated that the combination of two hyperosmotic agents (oral sulfate and diatrizoate) are comparable. In order to increase the value of this manuscript I would like the authors explain: 1) Why they use clear liquid diet instead low-fiber diet, because the combination of liquid diet and osmotic agents increase the incidence of adverse events; 2) To simplify the algorithm why do not avoid 2L of PEG prior to CE, why not oral sulfate solution?

Answer:

- Why was the diet liquid, instead of low-residue, the day prior to capsule colonoscopy? Our study builds on the work of many others, but in particular Rex, *Gastroenterology* 2015 and Spada, *Gut* 2017. Our study compares these prior preparation regimens to our Control and Study regimens. Rather than introduce an additional variable of diet, we utilized the same diet as had been used by these other investigators – clears the entire day prior. For colonoscopy, we agree with the reviewer that a low fiber diet (as least for breakfast, and possibly lunch and even later in the day) is better tolerated and not inferior to clears with respect to colon cleansing. Future studies should look at liberalizing the current standard capsule colonoscopy diet of clear liquids.
- Why not use oral sulfate solution on the morning of capsule ingestion rather than 2L PEG-ELS? There are 3 reasons this was not done: 1) avoiding too many new variables when building on past regimens, 2) avoiding high dose sulfate solution beyond that FDA-approved for colonoscopy, and 3) avoiding administration of sulfate solution over a shorter period of time than is FDA recommended.

1. The primary regimens our Study and Control regimens were based upon used split dose 4L PEG-ELS before capsule ingestion. We evaluated low dose sulfate solution with or without diatrizoate solution for the first and second boost.
2. The recommended FDA-approved dose for sulfate solution for bowel purgation would be exceeded if split dose sulfate solution (and not split PEG-ELS) were the used pre-procedure (6 ounces in the PM, 6 ounces in the AM, and then 3-6 ounces for boosts would exceed the approved total of 12 ounces for colonoscopy).
3. If one were to use 2L PEG-ELS in the evening, and then 6 ounces of sulfate solution in the AM prior to capsule (which does not really simplify the regimen as 2 different purgatives are required), there would be the issue of administering too much sulfate solution over too short a period of time. The approved dosing of sulfate solution is 6 ounces in the PM, and then 6 ounces in the AM before colonoscopy with a 10-12 hour interval between doses. If sulfate solution were used for the AM dose before capsule ingestion, it would mean that up to 12 ounces of sulfate solution could be administered over as little as less than 5 hours (depending on both the speed of gastric emptying and the need for a second sulfate solution boost). Sulfate solution was studied for colonoscopy using evening dosing alone, but this was not approved by the FDA – possibly due to greater adverse events and/or greater electrolyte disturbances.

Reviewer #3 Comments to the Authors: I have no concerns about your manuscript. Although, in clinical practice I wonder if the proposed regimen for bowel preparation will be choose from several other protocols. I recommend your manuscript for publication. P.S. However, I have one observation: please, read carefully the Format for references and make corrections.

Answer:

- **Carly and/or Delila please see if this is indeed the case and make the changes; if not then let me know and I can address.**