Our point-by-point responses to each suggestion and comment are given below.

First, we modified the title of this manuscript as mentioned below to comply with the Guidelines for WJCC.

"Efficacy of 1.2 L polyethylene glycol plus ascorbic acid as bowel preparations"

Next, we added "BACKGROUND" to the Abstract, "Audio core tip", and "ARTICLE HIGHLIGHTS". Furthermore, we modified our statement for the study's "AIM" to comply with the Guidelines for WJCC.

BACKGROUND

A low-volume polyethylene glycol (PEG) solution that combines ascorbic acid with polyethylene glycol-based electrolyte solution (PEG-ASC) is gaining mainstream acceptance for bowel preparation due to reduced volume and improved taste. Although several reports showed that bowel preparation with PEG-ASC volume lower than 2.0 L with laxative agents could be alternative to traditional preparation regimen, the cleansing protocols have not been fully investigated.

AIM

To evaluate the cleansing efficacy of 1.2 L PEG-ASC solution comparing with 2.0 L PEG electrolyte (PEG-ELS) for bowel preparations.

To reviewer #1

1. Dose of sennoside not clear 12 or 48 mg?

As you suggested, we clarified the dose of sennoside. The sennoside dose in the "Study Procedures" and the "Discussion" was mistakenly described and 48 mg is true, so we changed the sentences as mentioned below in line 28 of page 9 (MATERIALS AND METHODS, study procedures) and in line 17 of page 15 (DISCUSSION).

"(2) 48 mg of sennoside was administered on the day before colonoscopy,"
"an instruction for patients to take low-residue diet and an administration of 48 mg of sennoside on the day before colonoscopy, followed by bowel preparation with 1.2 L of PEG-ASC and at least 0.6 L of additional clear fluid during procedure on the day of colonoscopy."

2. Preference of sennoside over bisacodyl? any reason.

We chose sennoside simply because the bisacodyl tablet is not available in Japan (only suppository is available). We consider that 48 mg of sennoside is suitable as a stimulant agent to combine with PEG solution.

3. Authors should comment about preparation to colonoscopy time interval.

We agree that the time interval between bowel preparation and the start of colonoscopy is a significant factor affecting the quality of bowel preparation. Therefore, we evaluated the time interval between the completion of bowel preparation and the start of colonoscopy. As a result, the time interval was significantly longer in the 1.2L PEG-ASC group than in the PEG-ELS group (147.3 ± 66.2 min vs. 115.9 ± 54.7 min, $P < 0.01$). In this study, we could not match the time interval strictly because of the time constraint for the schedule of colonoscopy, and this difference is thought to be due to the difference in the required time for bowel preparation between the two groups and fixed the starting time of colonoscopy in both groups.

Kim *et al*. reported the relationship in the time interval between the last PEG intake and the start of colonoscopy. Although they concluded that the optimal time was 5-6 hours for the full-dose PEG method, there was no significant difference between the time intervals under 3 hours and 5-6 hours in patients who received the PEG solution and colonoscopy on the same day. Therefore, in the current study, we consider that the difference of 30 minutes in the time interval between the two groups did not have a potent influence on the evaluation of the cleansing effect.

- ✓ We added the sentence as mentioned below in lines 21-22 of page 10 (MATERIALS AND METHODS)
  "…and the time interval between the completion of bowel preparation and the start of colonoscopy…."

- ✓ We added the sentence as mentioned below in lines 8-9 of page 11 (MATERIALS AND METHODS, End points)
  "…the time interval between the completion of bowel preparation and the start of colonoscopy…"

- ✓ We added these data in lines 14-15 of page 13 (RESULTS, Secondary Endpoints).
  "The time interval was significantly longer in the 1.2L PEG-ASC group than in the PEG-ELS group (147.3 ± 66.2 min vs. 115.9 ± 54.7 min, *P* < 0.01)."

- ✓ We added the sentence below in line 17 to line 32 of page 16 (DISCUSSION)
  "The time interval between the bowel preparation and the start of colonoscopy was reported as one of the predicting factors affecting bowel cleansing effect as well as age, sex, diabetes, constipation, history of abdominal surgery, compliance with preparation instructions, and bowel preparation type. In the current study, the time interval was significantly longer in the 1.2L PEG-ASC group than in the PEG-ELS group (147.3 ± 66.2 min vs. 115.9 ± 54.7 min, P < 0.01). This difference is considered to be due to the difference in the required time for bowel preparation between the two groups and fixed starting time of colonoscopy in both groups. Kim et al. reported the relationship in the time interval between the last PEG intake and the start of colonoscopy [44]. Although they concluded that the optimal time interval was 5-6 hours for the full-dose PEG method, there was no significant difference in the cleansing effect between the time intervals under 3 hours and 5-6 hours in the patients who received the PEG solution and colonoscopy on the same day. Therefore, we considered that the difference of 30 minutes in the time interval between the two groups in the

current study did not have a potent influence on the evaluation of the cleansing effect."

- ✓ We referred to the manuscript mentioned below.

  "44. Kim TK, Kim HW, Kim SJ, Ha JK, Jang HH, Hong YM, Park SB, Choi CW, Kang DH. Importance of the time interval between bowel preparation and colonoscopy in determining the quality of bowel preparation for full-dose polyethylene glycol preparation. Gut Liver 2014;8:625–31 [PMID: 25368750 DOI: 10.5009/gnl13228]"

4. Discussion- page 28 =(Although this phenomenon has had no known cause yet, some differences in dietary habit, body dimensions, or reactivity for the cleansing agent affect colonic transit time may have been at play) Recent study from south Asia also showed optimal preparation with combination of stimulant laxative and low dose preperation (Ref. Polyethylene glycol plus bisacodyl: A safe, cheap, and effective regimen for colonoscopy in the South Asian patients). The effects of dietary habit and colonic transit time on colonoscopy preparation in Asian patients may explains these difference?

Thank you for your thought-provoking comment. We have to emphasize that the combination of PEG-ASC and laxative is critical to exert the volume-sparing effect. The combination of PEG-ASC lower than 2 L plus bisacodyl or sennoside are thought to be effective in the population who are successfully treated with 2 L PEG-ELS plus laxative, and body dimensions, diet habits, and bowel transit time, etc., vary among population and are considered to affect the reactivity for cleansing agents.

- ✓ We modified the sentences as mentioned below in line 20 of page 14 to line 1 of page 15 (DISCUSSION).

  "Traditional 4 L PEG regimen is widely accepted as a first recommended regimen for its safety and efficacy. However, ingestion of the large volume of solution and its unpleasant taste may result in poor acceptability and

adherence. To improve these limitations, low-volume regimens that combine PEG and osmotic agents (e.g., ascorbic acid, sodium phosphate) or stimulant agents (e.g., bisacodyl, sennoside) are developed. Several studies compared 2 L PEG-ASC and traditional 4 L PEG regimen and concluded that 2 L PEG-ASC had comparable cleansing efficacy with better acceptability[27,36]. In contrast, 2 L PEG regimen combined with bisacodyl was reported to have comparable cleansing effect to traditional 4 L PEG regimen[37,38]. Furthermore, several groups in East Asia recently reported that the combination of PEG-ASC and bisacodyl or sennoside reduced the volume of the cleansing solution to 1 or 1.5 L with comparative cleansing effect and improved patient acceptability to 2 L PEG regimen combined with laxative or split-dose 2-L PEG-ASC."

- ✓ We modified the following in line 24 to 31 of page 17 (DISCUSSION).

  "They can vary in effectiveness depending on the racial or regional groups because body dimensions, diet habits, and bowel transit time, etc., vary among population and are considered to affect reactivity for cleansing agents. Although the efficacy of the combination of PEG-ASC lower than 2 L plus bisacodyl or sennoside was currently evaluated only in East Asia, they are thought to be effective in the population who are successfully treated with 2 L PEG-ELS plus laxative (e.g., South Asia [37] or Canada [38])."

- ✓ We referred to the manuscripts mentioned below.

  "37. Jha AK, Chaudhary M, Jha P, Kumar U, Dayal VM, Jha SK, Purkayastha S, Ranjan R, Mishra M, Sehrawat K. Polyethylene glycol plus bisacodyl: A safe, cheap, and effective regimen for colonoscopy in the South Asian patients. JGH Open 2018;[DOI: 10.1002/jgh3.12077]"

  "38. Brahmania M, Ou G, Bressler B, Ko HK, Lam E, Telford J, Enns R. 2 L versus 4 L of PEG3350 + electrolytes for outpatient colonic preparation: a randomized, controlled trial. Gastrointest Endosc 2014;79:408–416.e4 [PMID: 24206747 DOI: 10.1016/j.gie.2013.08.035]"

5 Minor language problem

We obtain English proofreading by a language editing service again. The revisions that we have made to the revised manuscript are underlined in the updated version of the manuscript.

To reviewer #2

1. The study is well prepared and well written and definitely it is worth to be published. The authors appropriately stressed that 1.2 L PEG-ASC solution and sennoside with prior-residue diet is a suitable alternative to the Japanese standard because the results may differ for other populations. It looks that investigated groups did not differ in terms of comorbidities which could have an impact for bowel prep (diabetes, constipation). However, it would be great if the authors would like to write that no statistical differences in both groups in terms of indications for colonoscopy (especially I concern about altered bowel habit to lose and more frequent stools where I think a good prep might be achieved more easily).

Thank you for your comments. As you mentioned, indications for colonoscopy are important information when we discuss the efficacy of bowel cleansing regimens. Therefore, we added the data of indications for colonoscopy and the results of statistical analysis between two groups at the latter part of Table 1. As a result, we found no difference in terms of the indications for colonoscopy between the two groups.

- ✓ We modified Table 1.

- ✓ We added the sentence below in line 27 to line 28 of page 12 (RESULTS, Clinical characteristics)

  "or indications for colonoscopy"

	1.2L PEG-ASC (n = 156)	PEG-ELS (n = 156)	Total (n = 312)	*P* value
Age (Mean, range)	62.6 (19-89)	63.5 (24-89)	63.0 (19-89)	0.21

Sex (Male, %)	93 (59.6)	84 (53.8)	177 (56.7)	0.30
Constipation: n (%)	39 (25.0)	38 (24.4)	77 (24.7)	0.89
Abdominal operation: n (%)	58 (37.2)	55 (35.3)	113 (36.2)	0.72
Hypertension: n (%)	36 (23.1)	26 (16.7)	62 (19.9)	0.16
Diabetes: n (%)	12 (7.7)	15(9.6)	27 (8.7)	0.54
Experience of colonoscopy: n (%)	89 (57.0)	87 (55.8)	176 (56.4)	0.81
Indications for colonoscopy: n (%)				
Occult blood test-positive	76 (48.7)	70 (44.9)	146 (46.8)	0.50
Surveillance	30 (19.2)	27 (17.3)	57 (18.3)	0.66
Screening	21 (13.5)	22 (14.1)	43 (13.8)	0.87
Blood in stool	10 (6.4)	13 (8.3)	23 (7.4)	0.52
Abdominal pain	5 (3.2)	6 (3.9)	13 (4.2)	0.76
Constipation	4 (2.6)	5 (3.2)	9 (2.9)	0.74
Diarrhea	2 (1.3)	5 (3.2)	7 (2.2)	0.44
Other reason	8 (5.1)	8 (5.1)	16 (5.1)	0.80

Table 1 Clinical characteristics

PEG-ASC: Polyethylene glycol plus ascorbic acid; PEG-ELS: Polyethylene glycol-based electrolyte solution.

2. I would be also interested to know if no difference with quality of bowel prep (1.2 L PEG-ASC vis 2.0 L of PEG-ELS) in patients with constipation. The answer could be relevant for potential guidelines in the future.

As you recommended, it is important to evaluate the cleansing efficacy according to various factors in each groups and compare them. Therefore, we provided additional evaluation comparing the successful cleansing rates according to several factors (age 70 years and older; female sex; constipation;

diabetes; and history of abdominal operation) between the two groups. In consequence, there was no significant difference in the successful cleansing rates between the two groups including patients with constipation.

✓ We added Table 3.

Table 3 Successful cleansing rates according to various factors

	1.2L PEG-ASC % (No.)	**PEG-ELS % (No.)**	***P* - value**
Age (70 years and older)	89.8 (44/49)	89.6 (43/38)	0.77
Sex (Female)	93.2 (55/59)	87.7 (57/65)	0.46
Constipation	81.1 (30/37)	88.6 (31/35)	0.58
Diabetes	83.3 (10/12)	81.3 (13/16)	0.72
History of abdominal operation	93.1 (54/58)	92.7 (51/55)	0.77

PEG-ASC: Polyethylene glycol plus ascorbic acid; PEG-ELS: Polyethylene glycol-based electrolyte solution.

✓ We added these sentences in line 24 to line 26 of page 13 (RESULTS, Secondary endpoints)

"Additionally, there was no significant difference in the successful cleansing rates according to various factors (age 70 years and older; female sex; constipation; diabetes; and history of abdominal operation) between the two groups (Table 3)."

3. Personally, I always advise patients before colonoscopy to drink more fluids than they pass during bowel prep (we also need to put into account amount of diuresis). There is no problem for young and middle-aged patients to drink a sufficient amount of fluid if they need it. I always worry about a dehydration in case of chronic renal failure (even with eGFR> 30) and senior patients. The last group used to present with decreased thirst – their perception of hypovolemia

and natural need to drink fluids can be impaired. I am not convinced that the authors' opinion "there were no significant changes in eGFR before and after the procedure" is a sufficient statement and I think they need to analyse the problem deeply.

We agree that dehydration and its related disease are serious complications to be considered when we administer PEG-ASC solution, especially to elderly patients or patients with renal dysfunction. As you mentioned, fluid replacement is an efficacious method to avoid them. In this study, patients were required to ingest at least 0.6 L of clear fluid as described in the "MATERIAL AND METHODS" section. In addition, they were encouraged to take additional clear fluid with no volume limitation.

We set 0.6 L as the minimum volume of clear fluid to be ingested during procedure in accordance with the suggestion by the drug package insert: half of the volume of the ingested PEG-ASC solution. However, sufficient fluid replacement, that is, more than 0.6 L, is considered to avoid intravascular volume depletion-related complications. Consequently, no fatal dehydration-related complications were observed in the current study. In addition, there were no significant changes in eGFR before and after the procedure in the 1.2 L PEG-ASC group. These results suggested that the volume of fluid intake was sufficient to maintain hydration in the 1.2 L PEG-ASC group. We discussed the risk of inducing intravascular volume depletion with PEG-ASC administration in the fifth paragraph of the "DISCUSSION." However, we have to describe the protocol and related results in detail and emphasize the importance of fluid replacement.

- ✓ We modified the sentences as mentioned below in line 1 to line 2 of page 17 (DISCUSSION).

  "…patients were encouraged to take additional clear fluid other than the required 0.6 L throughout the bowel-preparation process to maintain hydration."

- ✓ We modified the sentences as mentioned below in line 2 to line 14 of page 17 (DISCUSSION).

  "In this study, the minimum volume of clear fluid to be ingested during procedure was 0.6 L, which was in accordance with the instruction provided by the drug package insert: half of the volume of the ingested PEG-ASC solution. However, sufficient fluid replacement more than 0.6 L is considered to avoid intravascular volume depletion-related complications. Essentially, the total volume of fluid intake amounted to 2.23 ± 0.55 L suggesting that 1.03 ± 0.55 L of additional clear fluid was ingested by patients in the 1.2 L PEG-ASC group. Consequently, no fatal dehydration-related complications were observed in the current study. In addition, there were no significant changes in eGFR before and after the procedure in the 1.2 L PEG-ASC group (82.9 ± 1.9 mL/min·1.73 m^2 vs 81.5 ± 1.6 mL/min·1.73 m^2, P = 0.17; data not shown). These results suggested that the volume of fluid intake was sufficient to maintain hydration in the 1.2 L PEG-ASC group."

4. At the end of chapter entitled Study procedures the authors cannot write "… evaluating the cleansing effect in each colon segment: right, transverse, and rectosigmoid colon, … ". The splenic flexure is commonly recognised as the border between the right and left colon.

As you mentioned, the description "…right, transverse, and rectosigmoid colon…." was not appropriate to mention the broad region of the colon. We have to describe it as they have been written in the original manuscript (33 Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. /Gastrointest Endosc/ 2009; 69: 620-625 [PMID: 19136102 DOI: 10.1016/j.gie.2008.05.057]).

- ✓ We modified the sentences as mentioned below in line 31 to line 32 of page 10 (MATERIALS AND METHODS, Study procedures).

  "…the right colon (including the cecum and ascending colon), the transverse

colon (including the hepatic and splenic flexures), and the left colon (including the descending colon, sigmoid colon, and rectum).”

- ✓ We renamed the title of Table 2 and modified the word as mentioned below.
  “Successful cleansing rate according to colonic segment”
  “Left”

Regardless these discrepancies the authors study is a valid approach for many group of patients especially for these who need to have a colonoscopy and would not like to drink a lot of fluids. Maybe it is able to improve acceptability of colonoscopy as bowel cancer screening in some populations.

Thank you for your kind comments. We wish our manuscript were suitable and worthful to be published now.