Randomized clinical trial of a split-dose bowel preparation with 2L polyethylene glycol plus castor oil versus 1L polyethylene glycol plus castor oil and ascorbic acid before colonoscopy

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Abstract: Our aim was to evaluate efficacy and safety of 30mL CaO alone or plus Asc in bowel preparation before colonoscopy. Two hundred and forty six patients were allocated randomly to ingest 2L PEG with 30mL CaO, 1L PEG with 30mL CaO plus 5g Asc, or 3L PEG. We used Boston Bowel Preparation Scale (BBPS) to evaluate bowel preparation efficacy. We also determined other outcomes such as procedure time, polyp or adenoma detection rate and adverse events (AEs). Of 282 patients recruited, 36 were excluded. Groups were matched for baseline characteristics except weight (P = 0.020) and body mass index (BMI) (P = 0.003). Patient’s satisfaction were higher in 2L PEG-CaO (P = 0.016) and 1L PEG-CaO-Asc groups (P = 0.017). Patients’ compliance was 67.5%, 71.4% and 80.5% in 3L PEG, 2L PEG-CaO and 1L PEG-CaO-Asc groups (P = 0.014). Adequate bowel preparation rate was 75%, 78.57% and 53.66% in 3L PEG, 2L PEG-CaO and 1L PEG-CaO-Asc groups (P = 0.021). There were no differences in terms of remaining outcomes. Despite an increase in patients’ satisfaction and compliance, 1L PEG-CaO-Asc significantly decreased adequate bowel preparation rate. However, 2L PEG-CaO improved the patients’ satisfaction and compliance and increased adequate bowel preparation rate.

Keywords: Castor oil; Ascorbic acid; Bowel preparation; Polyethylene glycol

1. Introduction

Colorectal cancer (CRC) remains the major contributor to cancer-related morbidity and mortality[1]. Colonoscopy been considered to be the preferred tool for effectively screening and early treating CRC[2]. Issued data showed an approximate 50% reduction in mortality of CRC after resection of abnormal colonic lesions were performed by colonoscopy[3,4]. However, poor quality of bowel preparation will significantly decrease the efficacy and safety of colonoscopy procedure[5]. Published data suggested that inadequate bowel preparation was directly associated with more than 40% of colonoscopy failures[6]. Moreover, inadequate bowel preparation was related to lower polyp or adenoma detection rate[7], longer operation time[8], and higher risk of procedure related complications and incomplete colonoscopy rate[9].

To date, polyethylene glycol (PEG) solutions remain the preferred option of bowel preparation before colonoscopy[10]. However, required high volume of liquid obviously reduces patients’ tolerability and compliance[11]. Thus, adjunctive drugs such as bisacodyl and ascorbic acid have been added into PEG solutions in order to minimize the required volume of liquid[10,12]. However,
desired quality of bowel preparation has not already been achieved. Consequently, it remains an open question how to improve bowel preparation efficacy before colonoscopy.

Castor oil was derived from the seed of Ricinus communis and has been widely used as a safe and effective stimulant laxative for colon cleaning in many settings[13-16]. For example, Apisarnthanarak et al[13] detected comparative patients’ satisfaction and efficacy of colon cleansing between castor oil and sodium phosphate. Yang et al[16] unfolded that the laxative efficacy of castor oil was comparable with that of bisacodyl. It is noted that the regime of bisacodyl plus PEG[17] and the regime of sodium and phosphate[18] achieved desired quality of bowel preparation, decreased the required volume of liquid, and improved compliance with the recommended regime when compared to standard PEG regime. Moreover, study also suggested that 2L PEG containing ascorbic acid (Asc) obtained similar bowel preparation efficacy with 3L PEG[19], and which was superior to that of 2L PEG with NaP[20]. So, we rationally speculated that 2L PEG containing castor oil may have comparative efficacy with 2L PEG with bisacodyl or NaP in colon cleansing, and which is not inferior to high-volume 3L PEG regime. Moreover, two trials[21,22] suggested that 1L PEG with bisacodyl and Asc was associated with improved patient’s tolerability and desired quality of bowel preparation compared with 2L PEG with Asc. Consequently, we also speculated that CaO plus Asc may halve the required liquid of PEG solutions.

Previous studies[23-25] suggested a higher rate of adverse effects such as abdominal cramping, abdominal fullness, nausea, vomiting and insomnia after orally taken a large dose 50 or 60 mL of CaO. However, some trials found that low dose 30mL of CaO did not obviously increase the incidence of adverse events[13,26,27]. Thus, we hypothesized that 30mL of CaO may enhance colon cleansing of PEG, and 30mL of CaO plus Asc[28] may halve the required liquid volume of PEG. The aim of the present trial was to ascertain the efficacy and safety of low volume PEG with CaO and lower volume PEG with CaO plus Asc.

2. MATERIALS AND METHODS

2.1. Study design

A single-center, randomized, observer-blinded three-arm study was conducted from October 2017 to December 2018 at the endoscopy center at Chongqing University Cancer Hospital (Chongqing, China). In total, 80 patients received lower volume 1L PEG with CaO plus Asc (1L-PEG-CaO-Asc), low volume 2L PEG with CaO (2L-PEG-CaO), or traditional volume 3L PEG. At the time of registration, subjects were randomly assigned to one of three groups. They were randomized by a computer-generated list and were provided with written instructions. All patients provided written informed consent before taking part in the present study. We obtained ethical approval from the Ethics Committee of Chongqing University Cancer Hospital and Chongqing Cancer Hospital. The trial is registered at Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-IIR-17012418.

2.2. Patients

2.2.1. Inclusion criteria

Participants met the following criteria were considered: (1) age above 18 and under 75 years; (2) adult outpatients who will be scheduled to morning colonoscopy regardless of sex; (3) did not participate in other clinical trials which also aimed at investigating bowel preparation efficacy; (4) agree to participate, and give signed written informed consents.

2.2.2. Exclusion criteria

We excluded patients who met following criteria: (1) lactation; (2) pregnancy; (3) experienced the abdominal surgery such as gynecologic surgery, appendectomy, and laparoscopy; (4) neurological diseases; (5) contraindication of colonoscopy, (6) allergy to ingredients of PEG, castor oil or ascorbic acid or (6) other reasons that are considered to be unsuitable for study participation by the responsible investigators.

2.3. Colonoscopy preparation
According to the findings from our previous meta-analysis[29], all participants enrolled in our study were instructed to take low fat and residue diet without food color the day before colonoscopy examination, and all begin to fast at 20:00 pm on the day before colonoscopy examination. Patients were allowed eating bun, bread, and chocolate in order to enhance tolerance, decrease incidence of AEs such as hypoglycemia if they experienced serious hunger feeling. Moreover, investigators explained the purpose of colonoscopy and the importance of adequate bowel preparation before colonoscopy examination. In order to obtain adequate bowel preparation and take the fear away, investigators also explained the processes of bowel preparation for patients and the methods of processing all possible AEs associated with bowel preparation. Moreover, the study protocols of all 3 groups have been outlined in our published protocol[30].

2.4. Study Endpoints

2.4.1. Primary outcome

We defined the bowel preparation efficacy and adequate bowel preparation rate as the primary outcome in the present study[30]. We used the Boston Bowel Preparation Scale (BBPS) to evaluate the quality of bowel preparation[31]. BBPS is a comprehensive scoring system of evaluating bowel preparation efficacy before colonoscopy[31], and has been widely used in clinical practice worldwide[32,33]. Details of BBPS have been described in our published study protocol[30].

2.4.2. Secondary outcomes

We also measured cecal intubation time (endoscopists recorded the time of started colonoscopy examination until colonoscopy reached ileocecal part), withdraw time (endoscopists recorded the time of completely withdrew colonoscopy from anus), cecal intubation success rate (the proportion of successfully reached ileocecal part), detection rate of polyp and adenoma (the proportion of polyp and adenoma detecte in the whole colonoscopy procedure), patients’ satisfaction (patients answered the questioner through selecting yes or no), patients’ tolerability (patients expressed feeling with a Likert scale ranged from 1 (not good) to 4 (excellent)), patients’ willingness to repeat colonoscopy (patients expressed feeling to repeat colonoscopy through selecting yes or no), and quality of sleep (patients were instructed to self-evaluate the quality of sleep when compared to previous night’s sleep) as the secondary outcomes.

2.4.3. Safety assessments

The direct investigator recorded all AEs related to bowel preparation and colonoscopy such as abdominal fullness, abdominal pain, nausea, vomiting and others into the case report form. It is noted that any symptom that existed before the start of the bowel preparation was not be recorded as AEs.

2.5. Sample size and statistical analysis

The bowel preparation efficacy was primarily tested in the present study, and thus we calculated the anticipated sample size based on this outcome. Based on the findings from previous studies[19,21], we proposed that the rate of adequate bowel preparation in 3L PEG, 2L PEG with 30mL CaO, and 1L PEG with 30mL CaO plus Asc will be 85%, 90%, and 95%. We assumed the significance and power to be 0.05% and 80%, respectively, and thus the sample size required to detect a difference will be 255 patients according to the non-inferiority design. Because the dropout rate was expected to be 10%, each trial group will be made up of at least 94 participants.

Continuous variables were expressed as mean ± standard deviation (SD), and discontinuous variables were expressed as counts and percentages. Data were analysed on a Full Analysis Set basis with SPSS for Windows release 22.0 software (SPSS, Chicago, Illinois, USA). χ2 analysis or Fisher’s exact test was used for comparison of categorical data. Normally distributed continuous data were analyzed by means of one-way ANOVA. Kruskal–Wallis H test was used only for analysis of non-normally distributed data. Differences were considered significant at P < 0.050.

3. Results

3.1. Baseline characteristics
During the study period, a total of 282 consecutive patients were screened, but 36 patients were excluded due to various reasons. Therefore, 246 patients were randomized and included in the full analysis set (FAS). A flow diagram that describes patients' enrollment is depicted in Figure 1.

![Flow diagram](image)

Figure 1. CONSORT diagram for the trial. PEG, polyethylene glycol; CaO, castor oil; Asc, ascorbic acid.

The three groups were comparable in terms of age, sex, height, medical conditions, the indication for colonoscopy, previous colonoscopy, willingness to repeat colonoscopy and quality of sleep (Table 1). The weight \( p = 0.020 \) and body mass index (BMI) \( P = 0.003 \) in 3L PEG and 1L PEG-CaO-Asc groups were higher than that in 2L PEG-CaO group. The most common reasons for colonoscopy were abdominal pain/distention/discomfort, change in bowel habit, and post-polypectomy surveillance.

3.2. Primary Outcome

All methods showed no significant difference in terms of quality of bowel preparation scoring, with a mean (SD) total score of 6.95 ± 1.83 for the 3L PEG group, 7.29 ± 1.60 for 2L PEG-CaO-Asc group and 6.35 ± 1.83 for the 1L PEG-CaO-Asc \( P = 0.062 \). The analysis of the segmental (right, mid, and recto-sigmoid colon) BBPS scale showed no difference for the right side \( (2.26 ± 0.76 vs 2.27 ± 0.71 \) vs 1.97 ± 0.8), mid colon \( (2.26 ± 0.76 vs 2.44 ± 0.59 vs 2.08 ± 0.6) \) and recto-sigmoid colon \( (2.42 ± 0.60 vs 2.59 ± 0.59 vs 2.30 ± 0.74) \). Table 2 presents the results of bowel cleansing quality assessment based on the BBPS. Percent of adequate bowel preparation, defined as total BBPS score ≥ 6 was 75.0%, 78.57% and 53.6% in 3L PEG, 2L PEG-CaO and 1L PEG-CaO-Asc groups, and the difference was statistically significant \( p = 0.001 \) (Figure 2). Further analysis based on paired comparison found that 3L PEG \( P = 0.010 \) and 2L PEG-CaO \( P = 0.002 \) significantly increased the percent of adequate bowel preparation compared to 1L PEG-CaO-Asc regime. Moreover, the reasons for incomplete colonoscopy mainly were extremely poor preparation and intolerance, however the percent of extremely poor preparation in 1L PEG-CaO-Asc group was significantly higher than that in 3L PEG (7.3% vs 0.0%) and 2L PEG-CaO (7.3% vs 2.4%) groups.

### Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Total (n)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (B=84)</td>
<td></td>
<td></td>
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<tr>
<td>Group C (n=82)</td>
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</tbody>
</table>

*P values calculated using chi-square or ANOVA test.
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD, years)</td>
<td>48.98 ± 12.47</td>
<td>52.26 ± 12.07</td>
<td>52.66 ± 8.79</td>
<td>0.273</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 42 (52.5)</td>
<td>Female 38 (47.5)</td>
<td>Male 44 (52.4)</td>
<td>40 (48.8)</td>
</tr>
<tr>
<td>Height (mean ± SD, cm)</td>
<td>162.10 ± 8.53</td>
<td>161.62 ± 7.33</td>
<td>160.88 ± 7.15</td>
<td>0.771</td>
</tr>
<tr>
<td>Weight (mean ± SD, kg)</td>
<td>62.08 ± 11.23</td>
<td>58.39 ± 8.29</td>
<td>65.17 ± 12.72</td>
<td>0.020</td>
</tr>
<tr>
<td>BMI (mean ± SD, kg)</td>
<td>23.62 ± 3.92</td>
<td>22.31 ± 2.60</td>
<td>25.13 ± 4.34</td>
<td>0.003</td>
</tr>
<tr>
<td>Medical conditions, n (%)</td>
<td>No 54 (67.5)</td>
<td>58 (69.0)</td>
<td>50 (61.0)</td>
<td>0.510</td>
</tr>
<tr>
<td></td>
<td>DM 2 (2.5)</td>
<td>4 (4.8)</td>
<td>6 (7.3)</td>
<td>0.378</td>
</tr>
<tr>
<td></td>
<td>Hypertension 14 (17.5)</td>
<td>10 (11.9)</td>
<td>12 (14.6)</td>
<td>0.598</td>
</tr>
<tr>
<td></td>
<td>Cardiac disease 2 (2.5)</td>
<td>2 (2.4)</td>
<td>2 (2.4)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Multiple 4 (5.0)</td>
<td>0 (0.0)</td>
<td>4 (4.8)</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>Others 4 (5.0)</td>
<td>10 (11.9)</td>
<td>8 (9.8)</td>
<td>0.287</td>
</tr>
<tr>
<td>Indication for colonoscopy, n (%)</td>
<td>Diarrhea 4 (5.0)</td>
<td>6 (7.1)</td>
<td>2 (2.4)</td>
<td>0.378</td>
</tr>
<tr>
<td></td>
<td>Constipation 0 (0.0)</td>
<td>1 (0.0)</td>
<td>2 (2.4)</td>
<td>0.659</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain/distention/discomfort 30 (37.5)</td>
<td>38 (45.2)</td>
<td>44 (53.7)</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>Change in bowel habit 12 (15.0)</td>
<td>10 (11.9)</td>
<td>8 (9.8)</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>Change in stool characteristics 4 (5.0)</td>
<td>3 (3.6)</td>
<td>0 (0.0)</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>GI bleeding 0 (0.0)</td>
<td>4 (4.8)</td>
<td>2 (2.4)</td>
<td>0.171</td>
</tr>
<tr>
<td></td>
<td>Surveillance 14 (17.5)</td>
<td>12 (14.3)</td>
<td>8 (9.8)</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>Physical examination 6 (7.5)</td>
<td>2 (2.4)</td>
<td>10 (12.2)</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td>Others 10 (12.5)</td>
<td>8 (9.5)</td>
<td>6 (7.3)</td>
<td>0.537</td>
</tr>
<tr>
<td>Previous colonoscopy, n (%)</td>
<td>No 34 (42.5)</td>
<td>30 (35.7)</td>
<td>28 (34.1)</td>
<td>0.506</td>
</tr>
<tr>
<td>Satisfied with bowel preparation, n (%)</td>
<td>Very good / good 70 (87.5)</td>
<td>82 (97.6)</td>
<td>80 (97.6)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>General/not good 10 (12.5)</td>
<td>2 (2.4)</td>
<td>2 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Completion of bowel preparation, n (%)</td>
<td>No 6 (7.5)</td>
<td>2 (7.1)</td>
<td>0 (0.0)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Yes 74 (92.5)</td>
<td>82 (92.9)</td>
<td>82 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Willingness to repeat colonoscopy, n (%)</td>
<td>No 26 (32.5)</td>
<td>24 (28.6)</td>
<td>16 (19.5)</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>Yes 54 (67.5)</td>
<td>60 (71.4)</td>
<td>66 (80.5)</td>
<td></td>
</tr>
<tr>
<td>Quality of sleep, n (%)</td>
<td>No change 26 (32.5)</td>
<td>30 (35.7)</td>
<td>40 (48.8)</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td>Worse 54 (67.5)</td>
<td>54 (64.3)</td>
<td>42 (51.2)</td>
<td></td>
</tr>
</tbody>
</table>

Group A, B and C represents 3L PEG, 2L PEG with CaO 30mL, and 1L PEG with CaO 30mL plus Asc 5g respectively. 3L PEG, 3L polyethylene glycol; 2L PEG with CaO 30mL, 2L polyethylene glycol with castor oil.
30mL; 1L PEG with CaO 30mL plus Asc 5g, 1L polyethylene glycol with castor oil 30mL plus ascorbic acid 5g. BMI, body mass index; SD, standard deviation.

*Statistical significance between groups was tested by one way ANOVA or Pearson χ² analysis (Fisher’s exact test if cell < 5).

![Proportion of bowel preparation efficacy in terms of each level among three groups.](image)

**Figure 2.** Proportion of bowel preparation efficacy in terms of each level among three groups.

*Statistical significance among these three groups was tested by χ² analysis for good/excellent group.

PEG, polyethylene glycol; CaO, castor oil; Asc, ascorbic acid.

### Table 2. Efficacy of bowel cleansing assessed by Boston Bowel Preparation Scale

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=80)</th>
<th>Group B (n=84)</th>
<th>Group C (n=82)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side of colon, (mean ± SD)</td>
<td>2.26 ± 0.76</td>
<td>2.27 ± 0.71</td>
<td>1.97 ± 0.87</td>
<td>0.172</td>
</tr>
<tr>
<td>Mid colon, (mean ± SD)</td>
<td>2.26 ± 0.76</td>
<td>2.44 ± 0.59</td>
<td>2.08 ± 0.68</td>
<td>0.072</td>
</tr>
<tr>
<td>Recto-sigmoid colon, (mean ± SD)</td>
<td>2.42 ± 0.60</td>
<td>2.59 ± 0.59</td>
<td>2.30 ± 0.74</td>
<td>0.145</td>
</tr>
<tr>
<td>Total score, (mean ± SD)</td>
<td>6.95 ± 1.83</td>
<td>7.29 ± 1.60</td>
<td>6.35 ± 1.83</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Group A, B and C represents 3L PEG, 2L PEG with CaO 30mL, and 1L PEG with CaO 30mL plus Asc 5g respectively. 3L PEG, 3L polyethylene glycol; 2L PEG with CaO 30mL, 2L polyethylene glycol with castor oil 30mL; 1L PEG with CaO 30mL plus Asc 5g, 1L polyethylene glycol with castor oil 30mL plus ascorbic acid 5g.

*Statistical significance between groups was tested by one-way ANOVA.

### 3.3. Secondary Outcome

Details of colonoscopy procedures are summarized in Table 3, the cecal intubation rate of all groups was >90%, the insertion time was about 6 minutes, and the average withdrawal time was >7 minutes. The endoscopic diagnoses of the three groups were comparable, about 20% of the patients had no abnormal findings, over 20% of the patients were found to have colitis, over 40% of the patients were found to have colorectal polyps, in addition, more than 55% of the polyps were adenomas. Only very few patients had cancer (3/246, 1.2%). Patients in 2L PEG-CaO and 1L PEG-CaO-Asc groups were more satisfied with the process of bowel preparation than patients in 3L PEG group (97.6% vs 97.6% vs 87.5%, p = 0.032). 92.5% and 92.9% patients in 3L PEG and 2L PEG-CaO
groups completed bowel preparation, whereas all the patients in 1L PEG-CaO-Asc group accomplished bowel preparation (p = 0.014). In addition, only 67.5% patients in 3L PEG group were willing to repeat colonoscopy in the endoscopy center if necessary, but 71.4% and 80.5% patients in 2L PEG-CaO and 1L PEG-CaO-Asc groups were willing to do so although significant results were not detected (P = 0.159). There was no significant differences in quality of sleep, the rates of abdominal fullness, abdominal pain, nausea, vomiting and other AEs among three groups (Table 4).

Table 3. Characteristics of the colonoscopy procedures

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=80)</th>
<th>Group B (n=84)</th>
<th>Group C (n=82)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal intubation success, n (%)</td>
<td>76 (95.0)</td>
<td>80 (95.2)</td>
<td>74 (90.2)</td>
<td>0.343</td>
</tr>
<tr>
<td>Reason for incomplete colonoscopy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely poor preparation</td>
<td>0 (0.0)</td>
<td>2 (2.4)</td>
<td>6 (7.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>Intolerance</td>
<td>2 (2.5)</td>
<td>2 (2.4)</td>
<td>1 (1.2)</td>
<td>0.871</td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.5)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0.214</td>
</tr>
<tr>
<td>Adequate bowel preparation, n (%)</td>
<td>60 (75.0)</td>
<td>66 (78.57)</td>
<td>44 (53.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cecal intubation time (min, mean ± SD)</td>
<td>7.84 ± 5.49</td>
<td>9.85 ± 12.75</td>
<td>10.19 ± 6.19</td>
<td>0.463</td>
</tr>
<tr>
<td>Withdraw time (min, mean ± SD)</td>
<td>6.26 ± 2.36</td>
<td>6.20 ± 3.44</td>
<td>6.62 ± 4.81</td>
<td>0.864</td>
</tr>
<tr>
<td>Medical results, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18 (22.5)</td>
<td>14 (16.7)</td>
<td>18 (22.0)</td>
<td>0.588</td>
</tr>
<tr>
<td>Polyps</td>
<td>8 (10.0)</td>
<td>20 (23.8)</td>
<td>16 (19.5)</td>
<td>0.063</td>
</tr>
<tr>
<td>Adenoma</td>
<td>26 (32.5)</td>
<td>25 (29.8)</td>
<td>24 (29.3)</td>
<td>0.891</td>
</tr>
<tr>
<td>Cancer</td>
<td>2 (2.5)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>0.323</td>
</tr>
<tr>
<td>Colitis</td>
<td>22 (27.5)</td>
<td>22 (26.2)</td>
<td>24 (29.3)</td>
<td>0.906</td>
</tr>
<tr>
<td>Others</td>
<td>4 (5.0)</td>
<td>2 (2.4)</td>
<td>1 (1.2)</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Group A, B and C represents 3L PEG, 2L PEG with CaO 30mL, and 1L PEG with Cao 30mL plus Asc 5g respectively. 3L PEG, 3L polyethylene glycol; 2L PEG with CaO 30mL, 2L polyethylene glycol with castor oil 30mL; 1L PEG with Cao 30mL plus Asc 5g, 1L polyethylene glycol with castor oil 30mL plus ascorbic acid 5g.

<sup>a</sup>Statistical significance between groups was tested by one way ANOVA or Pearson χ<sup>2</sup> analysis (Fisher’s exact test if cell < 5).

Table 4. Comparison of adverse event

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=80)</th>
<th>Group B (n=84)</th>
<th>Group C (n=82)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AE, n (%)</td>
<td>14 (18.0)</td>
<td>16 (19.0)</td>
<td>20 (24.0)</td>
<td>0.518</td>
</tr>
<tr>
<td>Abdominal fullness, n (%)</td>
<td>6 (8.0)</td>
<td>4 (5.0)</td>
<td>10 (12.0)</td>
<td>0.209</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>9 (11.0)</td>
<td>8 (10.0)</td>
<td>8 (10.0)</td>
<td>0.925</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>12 (15.0)</td>
<td>14 (17.0)</td>
<td>5 (6.0)</td>
<td>0.089</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>6 (8.0)</td>
<td>4 (5.0)</td>
<td>5 (6.0)</td>
<td>0.711</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Group A, B and C represents 3L PEG, 2L PEG with CaO 30mL, and 1L PEG with Cao 30mL plus Asc 5g respectively. 3L PEG, 3L polyethylene glycol; 2L PEG with CaO 30mL, 2L polyethylene glycol with castor oil 30mL; 1L PEG with Cao 30mL plus Asc 5g, 1L polyethylene glycol with castor oil 30mL plus ascorbic acid 5g. AEs, adverse event.

<sup>a</sup>Statistical significance between groups was tested by the Pearson χ<sup>2</sup> analysis (Fisher’s exact test if cell < 5).

4. Discussion
Although many novel and promising approaches have been proposed, colonoscopy remains a routine method of screening and early treating CRC[2]. However, the quality of bowel preparation will significantly affect the efficacy and safety of colonoscopy examination[5], and evidence suggests an about 25% of inadequate bowel preparation before colonoscopy[5]. It must be important to note that poor bowel preparation will also increase the rate of incomplete colonoscopy and adverse events and lower polyp and adenoma detection rate[34,35]. Thus, several methods have been proposed to improve the quality of bowel preparation[36-38]. Of these all methods, PEG solutions remain the first-line recommendation for bowel preparation prior to colonoscopy due to desire laxative efficacy[10], however required high volume of liquid will reduce tolerability and compliance to bowel preparation[11]. Thus, numerous studies have been performed to explore the potential of reducing the volume of the cleansing solution by adding adjunctive prokinetics such as bisacodyl[39,40], but the evidence suggests that gastrointestinal prokinetics can induce dose-dependent cardiac adverse effects[41]. So it is important to find a novel adjunctive laxative.

Castor oil is extracted from the seed of the castor-oil plant[42]. CaO has a high content of the hydroxylated unsaturated fatty acid ricinoleic acid[43], and it has been demonstrated that released ricinoleic acid has the ability of inducing strong laxative effect by activating small-intestinal smooth-muscle cells via the EP3 prostanoid receptor[44]. Moreover, CaO will not cause serious side effects[27], and thus it has been used as a safe stimulant laxative in many settings[45-47] except for pregnant women[48]. Evidence suggested low dose CaO (30 mL) has similar laxative efficacy of cleaning colon to bisacodyl[16]. Moreover, studies[26,27] also showed that 30mL of CaO can reduce liquid loading of bowel preparation solutions. And thus, we designed a regime of 2L split PEG with 30mL CaO to perform bowel preparation before colonoscopy. The findings of our randomized controlled trial suggested that 2L split PEG plus 30mL CaO can increase the adequate bowel preparation rate and patients’ satisfaction toward and patients’ compliance with regime with comparable BBPS score and AEs rate compared to traditional 3L split PEG solution.

A number of studies found that PEG with Asc regime obtained comparative efficacy, acceptability, tolerability, and safety related to the standard PEG regime[11,49-51]. Moreover, a recent meta-analysis also demonstrated the efficacy and safety of low-volume PEG containing Asc regime for bowel cleansing[52]. Asc produces cathartic effects because of it will become saturated at a high dose[53,54]. Asc contribute toward decreasing the total volume of PEG solution required for gut lavage and improve patient’s tolerability[27]. For these reasons, we have further designed a low-volume PEG preparation with 30mL CaO plus 5g Asc. The finding of our study showed that this modified lower-volume PEG regime obtained higher patients’ satisfaction and compliance. However, it is noted that this modified bowel preparation regime significantly decreased the adequate bowel preparation rate compared with traditional 3L split PEG regime. In the present study, patients with higher BMI were assigned to oral ingestion of 1L split PEG with 30mL CaO plus 5g Asc. Studies have found that high BMI is an independent factor associated with inadequate bowel preparation for colonoscopy[55-57]. This difference may be the contributor to the inconsistent finding. So, further study was needed in order to determine the adjunctive efficacy of combination of CaO and Asc.

We must acknowledge that our study has some limitations. First, we included patients who were schedule to morning and afternoon colonoscopy examination in this study. However, the time of colonoscopy did not have a significant difference among these three groups. Second, we performed this study in single-center and obtained results supported by insufficient number of patients. Thus, we suggest to design a multi-center study with larger scale to perform a more precise assessment. Third, evaluation of electrolyte levels or hematomal analysis was not carried out during the whole colonoscopy examination. However, we did not detect any significant difference in the rate of adverse events.

5. Conclusions

In conclusion, the results of this study indicate that the 30mL CaO in addition to 2L PEG before colonoscopy is safe, and it can improve patients’ satisfaction toward and compliance with the process of bowel preparation, increase the adequate bowel preparation rate, and obtain comparable quality of bowel preparation compared to 3L split PEG. Both preparation methods were effective. Patient’s adverse events and quality of sleep were similar between the 2 groups.
However, patients taking 1L PEG with 30mL CaO plus Asc 5mg in general showed more inadequate bowel preparation although it improved patients’ satisfaction and compliance related to 3L PEG regime.

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References


35. Clark BT, Tarun R, Loren L. What level of bowel prep quality requires early repeat colonoscopy: systematic review and meta-analysis of the impact of preparation quality on...


20. Rivas, J.M.; Perez, A.; Hernandez, M.; Schneider, A.; Castro, F.J. Efficacy of morning-only 4 liter sulfa


40. Masahiro; Tajika; Yasumasa; Niwa; Vikram; Hiroki; Kawai; Shinya; Kondo. Efficacy of mosapride citrate with polyethylene glycol solution for colonoscopy preparation. World Journal of Gastroenterology 2012, 18, 2517-2525.


53. Flavio; Valiante; Angelo; Bellumat; Manuela; Boni; Michele; Boni. Bisacodyl plus split 2-L polyethylene glycol-citrate-simethicone improves quality of bowel preparation before screening colonoscopy. *World Journal of Gastroenterology* 2013, 19, 5493-5499.


