Dried lemon slices improve the bowel cleansing quality of polyethylene glycol for colonoscopy preparation: Randomized controlled trial

[Study population (N=521)]

**RANDOMIZATION**

- The PEG group
  - N=254
- The PEG + lemon slices group
  - N=267

Primary outcome: BBPS score

Secondary outcome: adverse effects, defecation frequency and time consumed to finish laxatives, Patient acceptability, satisfaction, and willingness to repeat the same bowel preparation process.

- Dried lemon slices combined with conventional polyethylene glycol treatment showed higher quality of bowel cleanliness compared with conventional treatment for bowel preparation.
- Dried lemon slices improved the taste of laxatives and showed higher satisfaction among participants.
- Participants in the PEG + lemon slices group showed higher willingness to repeat the bowel preparation process.

Huang, et al.

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Dried lemon slices improve the bowel cleansing quality of polyethylene glycol for colonoscopy preparation: randomized controlled trial

Xiawei Huang, Liping Yang, Yingbo Lyu, Han Ma, Xiaoli Zhou, Kexin Ye, Jiehui Feng

**Abbreviations list**

PEG, polyethylene glycol
Asc, ascorbic acid
BBPS, Boston bowel preparation scale

**Disclosures**

**Conflicts of Interest and Source of Funding:** This study was funded by the Department of Education of Zhejiang Province of China, No. Y202043367. All authors report no
other relevant conflicts of interest for this article.

**Ethics approval**: This study was reviewed and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 143/2021).

**Clinical trial registration statement**: This study was registered at the Chinese Clinical Trial Registry (registration number: ChiCTR2200067215).

**Consent to participate**: All study participants provided verbal and written informed consent prior to study inclusion.

**Consent to publish**: Patients signed informed consent regarding publishing their data.

**CONSORT 2010 statement**: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

**Abstract**

**BACKGROUND**: Adequate bowel preparation is related to the quality of colonoscopy. Dried lemon slices can increase gastrointestinal peristalsis, which has shown potential as an adjuvant of bowel preparation. We hypothesized that the combination of dried lemon slices and PEG could improve the efficacy of bowel preparation and be more acceptable to participants.

**AIM**: To investigate the effectiveness of lemon slices combined with PEG for colonoscopy preparation.

**METHODS**: This study was a prospective, single-center, randomized, controlled trial of
521 patients randomly assigned to two groups. A total of 254 patients were given lemon slices based on conventional 4-L PEG treatment for the bowel, while 267 patients received only 4-L PEG treatment. Patients’ basic information, procedure-related parameters, adverse effects, and subjective feelings were collected by questionnaires. Intestinal tract cleanliness was scored according to the Boston bowel preparation scale (BBPS) by experienced endoscopists. Data were analyzed by the two-sample t-test or the chi-square test.

RESULTS: The BBPS scores were significantly higher in the PEG + lemon slice group (P < 0.05). The taste acceptability, satisfaction, and willingness to repeat bowel preparation were significantly higher in the PEG+ lemon slice group (P < 0.05). However, a larger proportion of patients from the PEG+ lemon slice group (30.7%) suffered from abdominal distension compared with the PEG group (20.6%), while the incidence of other adverse effects was comparable between the two groups.

CONCLUSION: The addition of dried lemon slices to conventional PEG showed its superiority for bowel preparation.

Keywords: Colonoscopy. Citrus. Polyethylene glycols. Laxatives.

Lay Summary: Colonoscopy is widely used in clinical practice, however, many patients suffer from the bowel preparation process before colonoscopy. In this study, we aimed to investigate the effectiveness of lemon slices combined with PEG for colonoscopy preparation, which could possibly improve the taste of laxatives and make patients feel better during the process. We randomly divided participants into two group to received conventional bowel preparation formula and new formula with lemon slices separately. The bowel preparation quality, adverse effects and patients’ objective feelings were evaluated during or after the process. The application of lemon slices combined with conventional polyethylene glycol treatment provided a novel method for bowel preparation with higher quality of bowel cleanliness compared with conventional treatment. In addition, it improved the taste of laxatives and showed higher acceptability. Hence, it is a practical and simple bowel preparation method.
demonstrating its prospect in clinical practice.

INTRODUCTION

As an efficient endoscopic technique, colonoscopy is widely used in clinical practice. To accomplish a high-quality colonoscopy, proper bowel preparation is necessary before the procedure[2]. Insufficient bowel preparation can result in a higher risk of misdiagnosis, increased rates of complications, and even postcolonoscopy colorectal cancer[2]. Osmotic laxatives, such as polyethylene glycol (PEG) are widely used for bowel preparation[3]. However, many patients suffer from the unpleasant flavor of PEG and adverse effects, such as nausea and vomiting. This unpleasant process ultimately leads to poor patient compliance and influences the quality of colonoscopy. Hence, improving the flavor of laxatives and reducing adverse effects is critical for qualified bowel preparation[4].

Compared with the standard PEG bowel preparation method, previous studies demonstrated the advantages of some adjuvants (e.g., orange juice, Gatorade) for improving the palatability of PEG and reducing unpleasant events, such as nausea[8][9]. Dried lemon slices are not only appetizing but can also trigger the secretion of proteases in the stomach, increase gastrointestinal peristalsis and improve digestion[10], which are potential adjuvants of laxatives. However, the effect of dried lemon slices on bowel preparation has not been clarified. The current study aimed to investigate the effectiveness of lemon slices combined with PEG for colonoscopy preparation. A total of 521 patients were recruited for this study and were randomly divided into two groups: the PEG+ lemon slice group and the PEG alone group. The PEG + lemon slice group was given dried lemon slices based on conventional PEG treatment to investigate the effect of lemon slices on bowel preparation. We hypothesized that the combination of dried lemon slices and PEG could improve the efficacy of bowel preparation and be more acceptable to participants.

MATERIALS AND METHODS

Study registry and approval
This study was registered at the Chinese Clinical Trial Registry (registration number: ChiCTR2200067215, URL: https://www.chictr.org.cn) This study was reviewed and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 143/2021).

**Study participants**

The enrollment, randomization, allocation and analysis process of this study is demonstrated in Figure 1. Patients aged 18 to 90 years old who underwent endoscopic treatment in the Department of Gastroenterology of Zhejiang University from October 2020 to February 2021 were assessed for eligibility. Patients who refused the procedure or who had contraindications to colonoscopy or bowel preparation (e.g., obstruction or perforation of the intestinal tract, toxic megacolon, disturbance of consciousness, allergy to the drug components, inability to swallow voluntarily, ileostomy status, gastric retention, severe active inflammatory bowel disease) were excluded. All subjects were informed of the study plan and were competent to complete the relevant investigation. According to the randomization table generated by the computer, the patients were randomly allocated 1:1 into two groups: the control group (PEG group) and the experimental group (PEG + lemon slice group). Participants were given verbal or written instructions about the procedure by the study nurse. Informed consent forms were signed by both groups before the procedure.

**Laxatives**

Dried lemon slices were purchased from the local market (trade name: Freeze Dried Lemon slices, Cheng-An Pharmaceutical Co., Ltd.). For each laxative solution, dried lemon slices of approximately 6 g were prepared. Compound sodium sulfate PEG powder was kindly provided by the First Affiliated Hospital, College of Medicine, Zhejiang University. Simethicone emulsion (trade name: Percy, Germany Berlin Chemical Co., Ltd.) with a total volume of 30 ml was used in this trial, and each milliliter of this product contained 40 mg of simethicone.
**Bowel preparation procedures**

Drug preparation was performed according to the drug instructions and 2019 update to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines on bowel preparation for colonoscopy[11]. Diet preparation was conducted according to the Chinese guidelines for bowel preparation for endoscopy[12]. Patients were all fed a low-residue diet the day before endoscopy procedures. Laxatives were prepared 6 to 7 hours in advance and packed in opaque containers by a designated nurse who was not allowed to contact the participants.

For the PEG group, 2 boxes of compound sodium sulfate PEG powder, with a volume of 4000 ml after dissolution in warm water, were taken within three hours. Subsequently, 15 ml of simethicone was taken, and the remaining 15 ml was taken 15 minutes before the colonoscopy.

For the PEG + lemon slice group, after the dissolution of PEG, approximately 6 g of lemon slices were added for a total volume of 4000 ml. Participants were asked to take the laxatives within three hours. Subsequently, 15 ml of simethicone was taken, and the remaining 15 ml was taken 15 minutes before the colonoscopy.

The endoscopists were physicians who had performed more than 1000 colonoscopies and were familiar with the BBPS scoring system. All endoscopists and nurses who directly contacted patients, as well as the staff who collected and analyzed the data, were blinded to the grouping and bowel preparation methods.

**Data collection**

The following data were collected after bowel preparation in the ward, including demographic characteristics, detailed procedures of bowel preparation (*e.g.*, the total volume of laxatives consumed, start and end times, defecation frequency), adverse effects (*e.g.*, nausea, vomiting, abdominal pain, bloating and dizziness), and subjective feelings (*e.g.*, acceptability of taste, overall satisfaction of bowel preparation, willingness to repeat the same bowel preparation).

Acceptability, satisfaction and willingness were graded on a 5-point scale separately.
The grading criteria were as follows:
1: Completely unacceptable/Very dissatisfied/Completely not willing;
2: Somewhat unacceptable/Dissatisfied/Not willing;
3: Somewhat acceptable/Moderately satisfied/Neutral;
4: Moderately acceptable/Satisfied/Willing; and
5: Completely acceptable/Very satisfied/Completely willing.
Colonoscopies were performed by skilled and single-blind endoscopists, and bowel cleanliness was evaluated according to the BBPS as described in previous study[13].

**Statistical analysis and sample size**
The power analysis was performed using G*Power (G*Power, version 3.1 for MAC, Dusseldorf, North Rhine-Westphalia). A sample size was determined to ensure an effect size difference of 0.30 in bowel preparation quality between the PEG + lemon slice group and the PEG group. With power of 0.80 and a 95% confidence interval, the sample size was calculated to be 184 subjects per arm. Considering a 10% drop rate, the sample size was 204 per arm.

Statistical software (SPSS, version 25.0 for MAC; SPSS, Chicago, IL), was used in this study. Categorical variables are presented as percentages and were analyzed using the chi-square test. Continuous data are presented as the mean and SD for Gaussian distributed values or medium and interquartile range for non-Gaussian distributed values. Student’s t test or the Mann-Whitney test was used to analyze continuous data. A P value < 0.05 was considered statistically significant.

**RESULTS**

*Patient characteristics*
From October 2020 to February 2021, after excluding 29 patients who refused the procedure, 521 patients were recruited. Participants were randomly assigned into two groups. A total of 254 subjects were allocated to the PEG + lemon slice group, while 267 subjects were allocated to the PEG group. No significant demographic differences were found between the PEG group and the PEG + lemon slice group (all p > 0.05,
Table 1).

**BBPS scores and procedure-related parameters**

The total BBPS score was significantly higher in the PEG + lemon slice group than in the PEG group (p < 0.05, Table 2, Figure 2). The time consumed to finish the procedure was comparable between the two groups, and no difference was found in the defecation frequency (both p > 0.05, Table 2). There was also no difference in the percentage of participants who drank the full amount of bowel preparation solution between the two groups (p > 0.05, Table 2), which means that patient compliance was not affected by lemon slices as adjuvants.

**Adverse effects**

No severe adverse events were reported in either group. However, the percentage of abdominal distension was significantly higher in the PEG + lemon slice group (p < 0.05, Table 2).

**Acceptability, satisfaction and willingness to repeat bowel preparation**

Compared with the PEG group, patient acceptance of the taste, satisfaction and willingness to repeat the same bowel preparation process were significantly higher in the PEG + lemon slice group (p < 0.05, Figure 2).

**DISCUSSION**

This study investigates bowel preparation using 4 L of PEG plus dried lemon slices to enhance bowel cleansing effects, improve the acceptability and satisfaction of the process. We found that using lemon slices as adjuvants can achieve a higher quality of bowel cleanliness and higher patient acceptability as well as satisfaction.

The result of improved quality of bowel preparation was consistent with previous studies. A previous meta-analysis that evaluated the effects of various adjuvants showed more adequate bowel preparation in the adjuvant group[14]. An earlier study showed better bowel cleansing efficacy of ascorbic acid treatment for bowel
Various adjuvants have been used in previous studies to improve palatability and patient acceptability [14]. Palatability has been surveyed in some trials using orange juice, pineapple juice, menthol candy drops, or even Coke Zero to mask the unpleasant taste of laxatives, and encouraging results have been reported[8][14][18]. The acceptability of taste was also improved in this study after adding lemon slices. Palatability is an important factor of satisfaction and contributes to the willingness to repeat bowel preparation. Higher willingness was found in the PEG + lemon slice group, consistent with previous studies using other adjuvants[14]. Lemon slices are enriched with ascorbic acid and are affordable, safe, easily obtained, and widely accepted by people. As common food in daily life, lemon slices are usually safe to be used as adjuvants after excluding an allergic history. Kim SH et al. showed that the safety of the 2-L low-volume PEG formulation containing ascorbic acid was not significantly different from that of the traditional 4-L PEG formulation[7], demonstrating the safety of using ascorbic acid in bowel preparation. However, the occurrence rate of abdominal distension was slightly higher in the PEG + lemon slice group. Similar adverse effects have never been reported before. An earlier randomized, controlled trial about ascorbic acid reported comparable complaints about abdominal distension[16], while some studies have shown reduced adverse events by adding ascorbic acid[15]. In the current study, although the proportion of abdominal distension slightly increased, no severe adverse events were reported. Previous studies have already proved the benefits of 2-L low-volume PEG formulation adding ascorbic acid[7], now we enumerate several advantages of lemon slices over ascorbic acid. Firstly, lemon slices are more affordable as a common food in daily life. Secondly, adding food but not a drug may make patients feel better and improve the compliance.

One strength of our study is that it was the first randomized, controlled trial to assess the efficacy and safety of lemon slices combined with PEG for inpatients undergoing a colonoscopy. Second, a total of 521 participants were enrolled in this trial, providing convincing results. However, there are still limitations to this study. First, only one scoring system was used in this study to evaluate the quality of bowel preparation.
Second, further safety data are needed to confirm the safety of using lemon slices, for example, blood sampling. Third, this study was a single-center study. Few domestic studies have shown the effectiveness of lemon slices combined with PEG in bowel preparation. Based on our findings, we suggest performing a multicenter, prospective, randomized, controlled trial to further explore or even popularize an optimized and accurate solution for intestinal preparation that is suitable for the Chinese population.

CONCLUSION
The bowel preparation method of PEG combined with lemon slices showed superiority in bowel cleanliness, patient acceptability and satisfaction, and it could be promoted as an efficient bowel preparation regimen.

Acknowledgment
This work was supported by the Department of Education of Zhejiang Province of China, No. Y202043367.
REFERENCES


2019;51(8):775–94.


Table 1 Patient characteristics
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PEG + lemon slice group</th>
<th>PEG group</th>
<th>Statistical values</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, M (P_{25}, P_{75}) )</td>
<td>58 (48, 66)</td>
<td>59 (50, 66)</td>
<td>0.510(^1)</td>
<td>0.610</td>
</tr>
<tr>
<td>Gender (total number, male/female)</td>
<td>254 (150/104)</td>
<td>267 (176/91)</td>
<td>2.618(^2)</td>
<td>0.106</td>
</tr>
<tr>
<td>Educational level (number (%))</td>
<td></td>
<td></td>
<td>3.677(^2)</td>
<td>0.720</td>
</tr>
<tr>
<td>Primary school</td>
<td>54 (21.3%)</td>
<td>61 (22.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior high school</td>
<td>80 (31.5%)</td>
<td>87 (32.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior high school</td>
<td>32 (12.6%)</td>
<td>42 (15.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior College</td>
<td>30 (11.8%)</td>
<td>25 (9.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University degree or above</td>
<td>46 (18.1%)</td>
<td>43 (16.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiteracy</td>
<td>12 (4.7%)</td>
<td>9 (3.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation (number (%))</td>
<td></td>
<td></td>
<td>8.402(^2)</td>
<td>0.395</td>
</tr>
<tr>
<td>Worker</td>
<td>20 (7.9%)</td>
<td>31 (11.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>28 (11%)</td>
<td>34 (12.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teacher</td>
<td>4 (1.6%)</td>
<td>7 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Civil servant</td>
<td>10 (3.9%)</td>
<td>7 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Businessman</td>
<td>22 (8.7%)</td>
<td>13 (4.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office clerk</td>
<td>30 (11.8%)</td>
<td>36 (13.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retiree</td>
<td>102 (40.2%)</td>
<td>96 (36.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>7 (2.8%)</td>
<td>12 (4.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>31 (12.2%)</td>
<td>30 (11.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td>0.318(^2)</td>
<td>0.853</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>16 (6.3%)</td>
<td>16 (6.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;23.9</td>
<td>112 (44.3%)</td>
<td>113 (42.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Annotation: 1) z value; 2) chi-square value

Table 2 BBPS scores, procedure-related parameters and adverse effects
<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>PEG + lemon slice group (254 patients)</th>
<th>PEG group (267 patients)</th>
<th>Statistical values</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defecation frequency (times (%) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>174 (68.8%)</td>
<td>190 (71.2%)</td>
<td>0.976²</td>
<td>0.614</td>
</tr>
<tr>
<td>&lt;6</td>
<td>25 (9.9%)</td>
<td>29 (10.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>54 (21.3%)</td>
<td>48 (18.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time consumed (hours, M (P₂₅, P₇₅) )</td>
<td>3 (2.5, 3.5)</td>
<td>3 (2, 3.4)</td>
<td>-1.421¹</td>
<td>0.155</td>
</tr>
<tr>
<td>Laxative use (number (%) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take all Laxatives</td>
<td>191 (75.2%)</td>
<td>208 (77.9%)</td>
<td>0.531²</td>
<td>0.466</td>
</tr>
<tr>
<td>Did not take all laxatives</td>
<td>63 (24.8%)</td>
<td>59 (22.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBPS score ( points M (P₂₅, P₇₅) )</td>
<td>8 (7, 8)</td>
<td>7 (7, 8)</td>
<td>-2.236¹</td>
<td>0.025</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (number (%) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15 (5.9%)</td>
<td>10 (3.7%)</td>
<td>1.330²</td>
<td>0.249</td>
</tr>
<tr>
<td>Negative</td>
<td>239 (94.1%)</td>
<td>257 (96.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache (number (%) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4 (1.6%)</td>
<td>4 (1.5%)</td>
<td>&lt;0.001²</td>
<td>1.000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (2.8%)</td>
<td>11 (4.1%)</td>
<td>0.726</td>
<td>0.394</td>
</tr>
<tr>
<td>Abdominal distension (number (%) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>78 (30.7%)</td>
<td>55 (20.6%)</td>
<td>6.998²</td>
<td>0.008</td>
</tr>
<tr>
<td>Negative</td>
<td>176 (69.3%)</td>
<td>212 (79.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Annotation: 1) z value; 2) chi-square value
**Figure 1** Flow diagram of enrollment, randomization, allocation and analysis of the PEG + lemon slice group and the PEG group. PEG: polyethylene glycol.

**Figure 2** (a) Dried lemon slices given to patients. (b) Quality of bowel preparation according to BBPS scoring system in both groups. (c-e) Acceptability, satisfaction, willingness to repeat bowel preparation were scaled by five degrees separately in both groups.

**Key Point Table**

<table>
<thead>
<tr>
<th>What previously known about this study</th>
<th>What this study contributes</th>
<th>How the results will influence clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acids could improve the bowel preparation quality when</td>
<td>Found out the bowel cleansing effects of lemon slices as adjuncts for</td>
<td>Provides a simple novel bowel preparation method with higher</td>
</tr>
<tr>
<td>used with PEG in bowel preparation.</td>
<td>bowel preparation.</td>
<td>quality of bowel cleanliness.</td>
</tr>
</tbody>
</table>
Found out the bowel cleansing effects of lemon slices as adjuncts for bowel preparation.

Using adjuncts such as orange juice could improve the palatability of laxatives and make patients feel better during the bowel preparation process.

Provided data on safety issues and adverse effects of using lemon slices for bowel preparation.

Provides a way to improve patient compliance and satisfaction during bowel preparation process.

Proved the palatability improving effects of lemon slices in the use of bowel preparation.