The Efficacy of 4 Liters of Clear Liquids for Small Bowel Preparation Prior to Video Capsule Endoscopy

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Background/Aims: Optimal small bowel (SB) preparation for video capsule endoscopy (VCE) is controversial. Our study aimed to support the use of a specified volume of 4 liters of clear liquids for bowel preparation for VCE.

Methods: A retrospective review of 284 patients who underwent SB preparation with 2 liters of polyethylene glycol (PEG) and 284 patients who had 4 liters of clear liquid preparation. We analyzed image quality, endoscopic findings, completion rate, and transit times.

Results: The 4-liter clear liquid group had significantly higher mean image quality scores when compared to the PEG group (2.669±0.64 to 2.908±0.77, \( p < 0.0001 \)), as well as more studies with adequate preparation (72\% to 64\%, \( p = 0.0214 \)). Although the PEG group had more endoscopic findings on VCE (40\% to 23\%, \( p < 0.0001 \)), there was a significant difference in the indications for the procedure between the groups. There was no difference in the capsule completion rate or SB transit time.

Conclusions: Our data demonstrate significantly higher mean image quality scores when using a specified volume of 4 liters of clear liquid compared to 2 liters of PEG. This study supports the growing evidence of the effectiveness of a 4-liter clear liquid SB preparation as opposed to PEG for VCE.

Key Words: Clear liquids; Polyethylene glycol; Small bowel preparation; Video capsule endoscopy
rated and had a similar diagnostic yield when compared to
the 2-liter and 4-liter PEG preparations.23 Hence, the ideal SB
preparation prior to VCE remains a controversial topic.
Our site previously conducted a randomized controlled
prospective non-inferiority trial comparing a specified volume
of 4 liters of clear liquid to 2 and 4 liters of PEG. The results
showed the 4-liter clear liquid preparation was non-inferior
in terms of image quality to both PEG groups and was better
tolerated with fewer reported side effects.22 The use of a speci-
fied volume of 4 liters of clear liquids may facilitate adequate
SB preparation. Since the completion of our study, we have al-
most exclusively used a 4-liter clear liquid preparation for VCE
studies at our center. We aim to corroborate our previously
collected data with a larger sample size in order to evaluate
whether 4 liters of clear liquid as an SB preparation for VCE
provides a comparable image quality to that of PEG.

MATERIALS AND METHODS
We conducted a retrospective review of consecutive out-
patient VCEs conducted from June 2011 to December 2012,
during which time a 2-liter PEG was exclusively used for SB
preparation. We compared these findings to VCEs conducted
from March 2017 to May 2018 when a 4-liter clear liquid SB
preparation was used. Patients are instructed to consume only
liquids which are clear, such as water, broth, sports drink, tea
etc. All patients in both groups received 30 mL of simethicone
prior to the procedure. PillCamTM Small Bowel capsule and
Rapid ReaderTM software was used in all patients in both
groups. Due to the lower completion rate for patients undergo-
ing VCE as inpatients as opposed to outpatients,23 we excluded
inpatient VCE. Data collected included patient demographics
(age, height, weight, sex, past medical history), indication for
procedure, gastric transit time (GTT), small intestine transit
time (SITT), image quality, and endoscopic findings.
Since only one clinician reviews VCE at our site, the image
quality for all procedures was reported by the same reviewer.
Image quality was graded on a scale of 1 to 4, with a score of 1
representing poor preparation, 2 fair, 3 good, and 4 excellent.
Mean image quality score and standard deviation between the
two groups were calculated. We also compared the proportion
of VCEs in each group that was considered to have “adequate”
preparation. Adequate preparation was defined as an image
quality score of 3 (good) or better. This qualitative scoring
system was validated by Brotz et al. for inter-observer and
intra-observer reliability and relies on the percent of mucosa
visualized, along with other factors including the degree of flu-
id and debris, bubbles, bile/chyme staining, and brightness.24

When the entire SB is evaluated, a score of good or excellent
requires >90% visualization of the mucosa throughout the
entire SB.24 Our primary outcome was image quality between the two
groups. Secondary outcomes were endoscopic diagnosis,
proportion of studies with adequate preparation, SITT, GTT,
and capsule completion rate. Statistical analysis was conducted
with a t-test using mean and standard deviation for continu-
ous variables and a Chi-squared test for categorical variables.
We set the significance at p < 0.05.

RESULTS
A total of 284 consecutive VCEs from June 2011 to Decem-
ber 2012 with the 2-liter PEG SB preparation and 284 con-
ssecutive patients from March 2017 to May 2018 who used the
4-liter clear liquid SB preparation were reviewed. Ten patients
in the clear liquid group and 8 in the PEG group were not in-
cluded in the analysis of image quality or endoscopic findings
due to the capsule staying in the stomach. An additional 10
patients were not included in the image quality analysis for the
PEG group because although endoscopic findings were re-
corded, the exam had insufficient transit of the SB to accurately
grade the overall image quality of the study. Therefore, 264
patients in the PEG group and 276 patients in the clear liquid
group were included in the image quality analysis and 274
patients in the PEG group and 276 patients in the clear liquid
group were included in the endoscopic findings data. GTT
time was not recorded for 24 patients in the PEG group and 18
in the clear liquid group due to the capsule staying in stomach,
endoscopic implantation of the capsule in the duodenum, or
a history of gastric bypass surgery, leaving n = 260 for the PEG
group and n = 266 for the clear liquid group for the calculation
of GTT. SITT was unable to be recorded in some incomplete
examinations, as well as in 4 additional patients in the PEG
group as it was unclear exactly when the capsule exited the SB.
Therefore, n = 249 for the PEG group and n = 252 for the clear
liquid group for the calculation of SITT.
There were no significant differences in the baseline charac-
teristics of the two groups (Table 1). However, the indications
for the procedure were significantly different between the two
groups. Specifically, the clear liquid group had statistically sig-
nificantly more examinations ordered for indications of ane-
mia and other, whereas the PEG group had significantly more
studies ordered to rule out SB tumor, evaluate for Crohn’s or
inflammatory bowel disease, or evaluate for arteriovenous
malformation (AVM) (Table 2). The preparation quality for the
PEG group and the clear liquids group was 2.669 ± 0.64
Table 1. Baseline Demographics of Patients

| Variables                        | 2 liters PEG (n=284) | 4 liters clear liquid (n=284) | p-value |
|----------------------------------|----------------------|-------------------------------|---------|
| Age (mean, SD)                   | 58.75±15.40          | 60.36±14.74                   | 0.204   |
| Sex, Male/Female, n (%)          | 112 (39)/172 (61)    | 108 (38)/176 (62)             | 0.730   |
| BMI (mean, SD)                   | 28.6±6.8             | 28.9±7.3                      | 0.613   |
| Prior abdominal surgery, n (%)   | 158 (56)             | 153 (54)                      | 0.673   |
| Diabetes mellitus, n (%)         | 84 (30)              | 74 (26)                       | 0.349   |
| Renal disease, n (%)             | 33 (12)              | 20 (7)                        | 0.061   |
| Liver disease, n (%)             | 17 (6)               | 25 (9)                        | 0.200   |

BMI, body mass index; PEG, polyethylene glycol; SD, standard deviation.

Table 2. Indication for Procedure

| Variables                             | 2 liters PEG (n=284) | 4 liters clear liquid (n=284) | p-value |
|---------------------------------------|----------------------|-------------------------------|---------|
| Anemia (n, %)                         | 158 (56)             | 185 (65)                      | 0.021   |
| GI bleed - Overt (n, %)               | 34 (12)              | 22 (8)                        | 0.091   |
| GI bleed - Occult (n, %)              | 4 (1)                | 5 (2)                         | 0.737   |
| Chronic abdominal pain (n, %)         | 34 (12)              | 30 (11)                       | 0.596   |
| Diarrhea (n, %)                       | 16 (6)               | 26 (9)                        | 0.109   |
| Rule out small bowel tumor/polyp (n, %) | 28 (10)             | 13 (5)                        | 0.015   |
| Suspect Crohn’s or IBD (n, %)         | 22 (8)               | 7 (3)                         | 0.004   |
| Rule out celiac disease (n, %)        | 10 (4)               | 4 (1)                         | 0.104   |
| Evaluate for AVM (n, %)               | 12 (4)               | 2 (1)                         | 0.007   |
| Malabsorption (n, %)                  | 1 (0)                | 1 (0)                         | 1.000   |
| Weight loss (n, %)                    | 0 (0)                | 5 (2)                         | 0.061   |
| Other (n, %)                          | 3 (1)                | 11 (4)                        | 0.030   |

Multiple indications possible for one procedure.

AVM, arteriovenous malformation; GI, gastrointestinal; IBD, inflammatory bowel disease; PEG, polyethylene glycol.

Table 3. Means and Standard Deviations for Small Bowel Preparation Quality, Gastric Transit Time, Small Intestine Transit Time, and Capsule Completion Rate

| Variables                              | 2 liters PEG           | 4 liters clear liquid        | p-value |
|----------------------------------------|------------------------|------------------------------|---------|
| Preparation quality, as Mean§          | 2.669±0.64             | 2.908±0.77                   | <0.0001 |
| (n=264)                                |                        | (n=276)                      |         |
| Number of exams with adequate prep¶    | 170 (64)               | 203 (72)                     | 0.0214  |
| (n=264)                                |                        | (n=276)                      |         |
| Gastric transit time in minutes¶       | 38.80±43.61            | 31.20±38.92                  | 0.0353  |
| (n=260)                                |                        | (n=266)                      |         |
| Small intestine transit time in minutes¶ | 222.0±79.94          | 225.1±90.26                  | 0.687   |
| (n=249)                                |                        | (n=252)                      |         |
| Capsule completion rate, n (%)         | 253 (89)               | 252 (89)                     | 0.894   |
| (n=284)                                |                        | (n=284)                      |         |

PEG, polyethylene glycol.

§Preparation quality measured 1 = poor; 2 = fair; 3 = good; 4 = excellent. ¶Preparation considered adequate if quality score 3 or greater. ¶Time measured in minutes.
and 2.908 ± 0.77, respectively (Table 2; p < 0.0001). Significantly more studies achieved an adequate preparation quality score in the clear liquid group than in the PEG group (Table 3; p < 0.05). There were no significant differences in the capsule completion rate or SITT, although the GTT was significantly longer in the PEG group compared to the clear liquid group (Table 3; p < 0.05). When comparing endoscopic diagnoses between the two groups, the PEG group had a greater percentage of clinically significant findings from VCE (40% to 23%, p < 0.0001), with more findings of AVMs (14% to 4%, p < 0.001) and non-specific mucosal flattening (5% to 0%, p = 0.001), whereas the clear liquid group had significantly more diagnoses of ileitis (7% to 3%, p = 0.017) (Table 4).

**DISCUSSION**

There remains a lack of consensus on optimal SB preparation prior to VCE. Meta-analyses have inconsistently shown the benefit of one preparation over another. While some meta-analyses of available data have shown that purgative bowel preparations with PEG or sodium phosphate have better image quality and diagnostic yield when compared to fasting or a clear liquid diet,11,14,17 a number of randomized control trials and meta-analyses have not reproduced these results.4,17,19 Furthermore, the mixed results of Yung et al. meta-analysis in 2017 showed no difference in diagnostic yield between the two bowel preparations, but it was noted that the purgative group had better image quality.17 The data from our study add to the growing evidence questioning whether bowel preparation with PEG is necessary prior to VCE. Our study showed improved image quality in the 4-liter clear liquid group when compared to the 2-liter PEG group, in addition to the higher proportion of VCE studies with adequate preparation quality in the clear liquid group. These results corroborate the data from two previously published randomized controlled trials that independently showed either the non-inferiority of or no significant difference between a 4-liter clear liquid preparation compared to PEG.21,22

An important consideration when choosing an SB preparation is patient tolerability and preparation compliance. Due to the retrospective nature of our study, we were unable to directly compare tolerability between the two groups. However, tolerability has been studied in two different randomized control trials. In a prospective study comparing 4 liters of clear liquid, PEG, and aqueous sodium phosphate by Pons Beltrán et al., tolerability was evaluated directly by patient questionnaire.21 The 4 liters of clear liquid preparation was associated with the least interference with patients’ daily activity and nocturnal rest (p = 0.001) and better compliance compared to PEG (p = 0.002).21 Another prospective study by Bahar et al. showed that patients who underwent a 4-liter clear liquid preparation had a lower difficulty of completion rate than those who underwent preparation with either 2 liters (p = 0.013) or 4 liters of

### Table 4. Endoscopic Diagnosis, Multiple Diagnoses Possible for a Single Study

| Endoscopic findings                              | 2 liters PEG (n=274) | 4 liters clear liquid (n=276) | p-value |
|--------------------------------------------------|----------------------|-------------------------------|---------|
| Normal small bowel (n, %)                        | 174 (64)             | 221 (80)                      | <0.0001 |
| AVM/angiodysplasia (n, %)                        | 38 (14)              | 10 (4)                        | <0.0001 |
| Active bleed (n, %)                              | 13 (5)               | 10 (4)                        | 0.511   |
| Small bowel polyp (n, %)                         | 14 (5)               | 6 (2)                         | 0.066   |
| Diverticulum (n, %)                              | 4 (2)                | 3 (1)                         | 0.697   |
| Inflammation (erosions, ulcers) of proximal to mid small bowel (n, %) | 19 (7)               | 13 (5)                        | 0.265   |
| Non-specific mucosal flattening (n, %)           | 13 (5)               | 1 (0)                         | 0.001   |
| Likely celiac disease (n, %)                     | 8 (3)                | 2 (1)                         | 0.054   |
| Suspected tumor (n, %)                           | 2 (1)                | 2 (1)                         | 0.994   |
| Stricture (n, %)                                 | 7 (3)                | 4 (2)                         | 0.355   |
| Ileitis (n, %)                                   | 7 (3)                | 19 (7)                        | 0.017   |
| Submucosal bulge (n, %)                          | 3 (1)                | 1 (0)                         | 0.312   |
| Clinically significant finding (n, %)            | 110 (40)             | 63 (23)                       | <0.0001 |

Multiple diagnoses possible for a single study.

AVM, arteriovenous malformation; PEG, polyethylene glycol.
PEG (p < 0.001), as well as a lower rate of side effects compared to those with 4 liters of PEG (p < 0.0167).22

In addition to overall image quality, it has been suggested that the advantage of using purgative preparations such as a PEG may lie in their ability to specifically improve image quality in the distal ileum.23 However, in addition to the overall better image quality scores, there were also significantly more diagnoses of ileitis in the clear liquid group than in the PEG group. Although the image quality of each section of bowel was not directly recorded in our study, based on the higher rate of finding ileitis in the clear liquid group, we can extrapolate that the distal SB preparation in the clear liquid group yielded an image quality adequate to diagnose lesions in the ileum.

Interestingly, our study demonstrated a greater number of endoscopic diagnoses in the PEG group than in the clear liquid group, despite the lower image quality in the PEG group. However, it is important to note when considering this result that there was also a significant difference in the indications for the procedure between the two groups, which likely led to this difference in endoscopic findings. For example, one notable difference between the groups was significantly more studies were ordered to evaluate the SB for AVMs in the PEG group, which likely contributed to the increased rate of endoscopic findings of AVM in the PEG group. This suggests that the higher number of endoscopic findings in the PEG group is attributable to differences in the indications for the procedure between the two groups and is not a reflection of image quality and differences in the quality of preparation. It is important to note, however, that the 4-liter clear liquid group had significantly more findings of ileitis despite having fewer procedures ordered specifically to rule out Crohn’s disease. Although we cannot say whether this was due to better image quality in the distal ileum, this finding further suggests that the greater number of endoscopic findings in the PEG group should not be interpreted as indicating better preparation or a higher diagnostic yield.

There are a few potential explanations for the difference in the indications for the procedure between the two groups. For our study, we wanted to review consecutive outpatient VCEs to minimize selection bias, which was difficult owing to the numerous different bowel preparations for VCE used between January 2013 and February 2017. Therefore, we selected date ranges during which only one bowel preparation regimen was used. We found that we exclusively used 2 liters of PEG prior to January 2013 and 4 liters of clear liquid after February 2017. The difference in the time period of the two groups may partially explain the significant differences in the indication for procedure as shown in Table 2.

One limitation of our study is that our institution has only one clinician who reads capsule endoscopies; therefore, we used a single reviewer with a standardized method and verification by multiple reviewers was not possible. Additionally, we used data that were recorded at the time of the capsule endoscopy and the endoscopist was not blinded to which preparation the patient had received. Although the 1–4 grading system we used to record image quality is widely used, it still has the potential for human error given its subjectivity. However, when validating this scoring method, Bro tz et al. found that its intra-observer reliability outperformed its inter-observer reliability and that reliability improved when comparing a score of adequate preparation (defined as a score of good or excellent) versus inadequate preparation (a score of poor or fair), which corroborates our decision to also compare these two groups.24 Development of objective methods to evaluate image quality in VCE has shown promise, such as computed cleansing scores,26,27 though they are not widely in use at this time. Future studies may benefit from using an objective tool to compare image quality between different SB preparations.

Optimal bowel preparation prior to VCE remains controversial. Although bowel preparation with PEG and other purgative solutions is commonly used, they are often poorly tolerated and inconsistently show superiority in terms of image quality and diagnostic yield compared to a clear liquid diet. Our current study demonstrates improved image quality with a specified volume of 4 liters of clear liquid compared to 2 liters of PEG as an SB preparation prior to VCE. These data further support our previously conducted randomized non-inferiority study,22 as well as the increasing evidence in favor of using 4 liters of clear liquid for SB preparation prior to VCE.

Conflicts of Interest

The authors have no financial conflicts of interest.

Author Contributions

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REFERENCES

1. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. Nature 2000;405:417.
2. Ladas SD, Triantafyllou K, Spada C, et al. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use
of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. Endoscopy 2010;42:220-227.

3. Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World J Gastroenterol 2013;19:3726-3746.

4. Hookey L, Louw J, Wiepjes M, et al. Lack of benefit of active preparation compared with a clear fluid-only diet in small-bowel visualization for video capsule endoscopy: results of a randomized, blinded, controlled trial. Gastrointest Endosc 2017;85:187-193.

5. Ninomiya K, Yao K, Matsui T, et al. Effectiveness of magnesium citrate as preparation for capsule endoscopy: a randomized, prospective, open-label, inter-group trial. Digestion 2012;86:27-33.

6. Hong-Bin C, Yue H, Chun H, Shu-Ping X, Yue Z, Xiao-Lin L. Randomized controlled trial of cholestyramine and hydrotalcite to eliminate bile for capsule endoscopy. Saudi J Gastroenterol 2016;22:122-126.

7. Stein DJ, Copland A, McDaniell D, Hays RA. Single-dose linacotide is equal in efficacy to polyethylene glycol for bowel preparation prior to capsule endoscopy. Dig Dis 2019;37:297-302.

8. Kim ES, Chun HJ, Koeum B, et al. Coffee enema for preparation for small bowel video capsule endoscopy: a pilot study. Clin Nutr Res 2014;3:134-141.

9. Niv E, Ovadia B, Ron Y, et al. Ensure preparation and capsule endoscopy: a two-center prospective study. World J Gastroenterol 2013;19:1264-1270.

10. Chen HR, Huang Y, Chen SY, et al. Small bowel preparations for capsule endoscopy with mannitol and simethicone: a prospective, randomized, clinical trial. J Clin Gastroenterol 2011;45:337-341.

11. Wu S, Gao YJ, Ge ZZ. Optimal use of polyethylene glycol for preparation of small bowel video capsule endoscopy: a network meta-analysis. Curr Med Res Opin 2018;34:1899-1906.

12. Enns RA, Hookey L, Armstrong D, et al. Clinical practice guidelines for the use of video capsule endoscopy. Gastroenterology 2017;152:1372-1379.

13. Catalano C, Companioni RA, Khankhanian P, et al. Video capsule endoscopy: is bowel preparation necessary? J Investig Med 2016;64:1114-1117.

14. van Tuyl SA, den Ouden H, Stolk MF, Kuipers EJ. Optimal preparation for video capsule endoscopy: a prospective, randomized, controlled study. Endoscopy 2011;43:406-411.