Split-Dose Preparations Are Superior to Day-Before Bowel Cleansing Regimens: A Meta-analysis

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this test, successful learners will be able to discuss the appropriate timing of administration of bowel preparation in split-dose bowel preparations, review the efficacy of different bowel preparation products when they are administered as a split preparations, and identify the efficacy of split-dose bowel preparation versus day-before bowel preparation for the same bowel preparation product.

BACKGROUND & AIMS: There are different regimens of preparing the colon for colonoscopy, including polyethylene glycol (PEG), sodium phosphate, picosulfate, or oral sulfate solutions. We performed a meta-analysis to determine the efficacy of split-dose vs other colon preparation regimens, the optimal products for use, and the most effective preparation volumes. METHODS: We performed systematic searches of MEDLINE, EMBASE, Scopus, CENTRAL, and ISI Web of knowledge databases, from January 1980 to March 2014, for published results from randomized trials that assessed split-dose regimens vs day-before colonoscopy preparation. We excluded studies that included pediatric or hospitalized patients, or patients with inflammatory bowel disease. The primary outcome was efficacy of bowel cleansing. Secondary outcomes included side effects or complications, outcomes of procedures, patients’ willingness to repeat the procedure, and the amount of time required for patients to resume daily activities. RESULTS: We identified 47 trials that fulfilled our inclusion criteria (n = 13,487 patients). Split-dose preparations provided significantly better colon cleansing than day-before preparations (odds ratio [OR], 2.51; 95% confidence interval, 1.86–3.39), as well as day-before preparations with PEG (OR, 2.60; 95% confidence interval, 1.46–4.63), sodium phosphate (OR, 9.34; 95% confidence interval, 2.12–41.11), or picosulfate (OR, 3.54; 95% confidence interval, 1.95–6.45). PEG split-dose preparations of 3 L or more yielded greater bowel cleanliness than lower-volume split-dose regimens (OR, 1.89; 95% confidence interval, 1.01–3.46), but only in intention-to-treat analysis. A higher proportion of patients were willing to repeat split-dose vs day-before cleansing (OR, 1.90; 95% confidence interval, 1.05–3.46), and low-volume split-dose preparations were better than high-volume split-dose preparation (OR, 4.95; 95% confidence interval, 2.21–11.10). There were no differences between preparations in other secondary outcome measures. However, there was variation among studies in definitions and main and secondary outcomes. CONCLUSIONS: Based on meta-analysis, split-dose regimens increase the quality of colon cleansing and are preferred by patients compared with day-before preparations. Additional research is required to evaluate oral sulfate solution-based and PEG low-volume regimens further.

Keywords: Meta-analyses; Bowel Preparation; Split-Dose; Bowel Cleansings.

High-quality colonoscopy increasingly is being associated with favorable patient outcomes in colorectal cancer screening initiatives1,2; adequacy of the preparation is one of its most important predictors,3 with the need for repeat procedures because of poor preparation carrying significant costs.4 The recent move toward split-dose and low-volume preparations coupled with the release of newer products in the United States have outdated most previous pertinent meta-analyses, justifying more contemporary systematic reviews. As part of many summary analyses informing recent recommendations by the Multi-Society Task Force (MSTF),5 we performed targeted meta-analyses determining the efficacies of day-before preparations vs split-dose regimens using contemporary used products, including polyethylene glycol (PEG), sodium phosphate (NaP), picosulfate (PICO), and oral sodium sulfate (OSS).

Materials and Methods

Search Strategy

Systematic searches were performed (January 1980 to March 2014) using MEDLINE, EMBASE, Scopus, CENTRAL, and ISI Web of knowledge. Citation selection used a highly sensitive search strategy identifying randomized trials6 with MeSH headings relating to the following: (1) colonoscopy, (2) gastrointestinal agents, (3) bowel preparation, and (4) generic and brand names (Appendix 1). Recursive searches, cross-referencing, and subsequent hand-searches were completed.

Abbreviations used in this paper: ITT, intention-to-treat; MSTF, Multi-Society Task Force; NaP, sodium phosphate; OR, odds ratio; OSS, oral sodium sulfate; PEG, polyethylene glycol; PICO, picosulfate; PP, per-protocol; WMD, weighted mean difference.
Trial Selection and Patient Population

All fully published randomized trials in French or English with at least 1 arm administering split-dose PEG, NaP, PICO, or OSS were included. Trials comprising only pediatric patients, in-patients, or inflammatory bowel disease patients were excluded.

Choice of Outcomes

The primary outcome measure was bowel cleanliness, defined as the proportion of patients with an adequate preparation. Anticipating heterogeneity in bowel cleanliness nomenclature across studies, preplanned dichotomization grouped excellent or good, as well as successful, optimal, and satisfactory, vs fair, poor, or insufficient bowel preparation cleanliness or mucosal visualization. We defined a product as PEG, NaP, PICO, or OSS alone, with or without an adjuvant such as senna, magnesium citrate, magnesium sulfate, magnesium oxide, mannitol, enema, olive oil, castor oil, bisacodyl, cisapride, domperidone, ascorbic acid, alverine citrate, lubiprostone, simethicone, probiotic, metoclopramide, mosapride, simethicone, or sodium ascorbate. Split-dose was defined as administration of product in 2 separate doses: the first dose was the day before and the second dose was the day of the colonoscopy, to minimize the duration of the interval between completion of the bowel preparation and the colonoscopy.

Day-before regimens referred to no dosage of the product given on the day of the colonoscopy. We excluded trial arms that assessed co-administration of 2 different products (combinations of PEG, NaP, OSS, and PICO).

The following comparisons were analyzed: split-dose vs day-before, and split-dose vs another split-dose. These analyses were performed in turn for all products combined, for a given product, or when comparing 2 different products.

Secondary outcomes included patient willingness-to-repeat the preparation, polyp or adenoma detection, side effects, or complications, empirically grouped according to hierarchical symptoms for clarity as follows: nausea or vomiting or nausea/vomiting; abdominal cramps or pain or spasm and discomfort or distress or bloating; insomnia or sleep disturbance; weakness or fatigue; fainting or dizziness; headache; chills; perianal irritation; and additional time required to resume daily activities.

Validity Assessment

Two investigators assessed citation eligibility with discrepancies resolved by an independent reviewer; consequent κ statistics were generated. The quality of trials was graded using the Cochrane risk bias tool and Jadad score6 (with 1 extra point for reported a priori sample size calculations). All data abstraction and entries were validated independently by 2 authors.

Sources of Possible Heterogeneity: Clinical and Statistical

Possible sources of clinical heterogeneity were noted across trials in keeping with preplanned sensitivity or subgroup analyses. Identification and handling of statistical heterogeneity is described later.

Statistical Methods and Sensitivity Analyses

For each outcome and in every comparison, effect size was calculated as odds ratios (ORs) for categoric variables and weighted mean differences (WMDs) for continuous variables. The Mantel–Haenszel method for fixed-effect models determined corresponding overall effect sizes with confidence intervals, except when statistical heterogeneity was noted, in which case a random-effects model was used according to the DerSimonian and Laird method.9 WMDs were manipulated using the inverse variance approach. Statistical heterogeneity across studies was defined using a chi-square test of homogeneity with a 0.10 significance level. The Higgins I² statistic was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity.10

Values for intention-to-treat (ITT) were preferred to per-protocol (PP) when both were presented. We included non-compliant patients or withdrawals in the ITT analysis to minimize bias.11

Preplanned sensitivity analyses assessing bowel cleanliness examined PEG split-dose of varying volumes vs a nonsplit dose. Additional dichotomization criteria were the use of a validated preparation cleanliness scale (Ottawa,12 Boston,13,14 Harefield15 Cleansing Scale, and Aronchick scores16), a publication date within the past 10 years, the inclusion of sole PP data, the geographic continent of study, and the type of diet (most dense diet for normal, liquid, low residue, or fasting) if similar in all arms on the precolonoscopy day. Finally, “good” bowel cleanliness may not be sufficient to detect lesions such as flat and sessile serrated adenomas and proximal polyps, an additional analysis with dichotomization for “excellent” or “optimal” bowel cleanliness was assessed. Only results including more than 3 trials were reported in sensitivity analyses.

As a final characterization of possible heterogeneity, we performed meta-regression using mixed-effects models and as successive dependent variables we used the following: year of publication, continent, and the diet followed for the preparation.

Publication bias was evaluated using the Begg adjusted rank correlation test17 and the Egger regression asymmetry test.18

All percentages of outcomes reported in the trials were converted to absolute numbers and no attempt at determining extractable values from graphics or figures was performed to avoid possible subjectivity.

To ensure zero event trials did not significantly affect the heterogeneity or P value, a continuity correction was added to each trial with zero events using the reciprocal of the opposite treatment arm size.19,20 All statistical analyses were completed using the Meta package in R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Included Studies

Overall, 2523 citations were retrieved; 2181 were rejected based on titles and abstracts, and 342 articles were fully reviewed (Figure 1). Nine trials21–29 were rejected from initial selection because 1 arm included both split and nonsplit dose regimens depending on the time of procedure,
making preplanned data extraction impossible. Forty-seven trials (13,487 patients) were included: 38 in the split-dose vs day-before, 30–67 and 12 for split-dose vs another split-dose comparisons41,52,59,67 (trials may appear in more than 1 comparison).

Inter-Rater, Heterogeneity, Publication Bias, and Study Quality

Inter-rater citation selection yielded a κ value of 0.76 (0.73;0.79). Moderate to strong heterogeneity was noted for the main outcome analyses except for PEG split-dose regimen vs PEG day-before comparisons. No publication bias was noted for the main outcome analyses according to Beggs and Eggers P values (Table 1).

Jadad modified quality scores ranged from 0 to 5 points (mean, 2.6 points) (Supplementary Table 1). The Cochrane risk bias tool showed a low potential for selection bias across studies. Only 1 study used a nonrandom component in the sequence generation process. Insufficient information on allocation concealment did not allow judging between high- or low-risk selection biases. Almost all trials were single-blinded but this was not considered a methodologic impairment. Other biases originated mainly from demographic imbalances (Figure 2).

Primary Outcome: Bowel Cleanliness

**Split-dose vs day-before.** Split-dose vs day-before regimen of any product. Thirty-eight trials30–67 (10,803 patients) compared split-dose with day before, regardless of product, dosage, or addition of adjuvant (Supplementary Table 1). Data on bowel cleanliness were not analyzable in 6 trials.35,38,45,48,54,67

A split-dose of any regimen significantly increased adequate preparations compared with day-before regimens (OR, 2.51; 1.86;3.39) (Figure 3 and Table 1).

PEG split-dose vs PEG day-before regimen. Thirteen trials (4083 patients) compared PEG split-dose vs PEG day-before preparations.31,32,34,35,39,41,42,51,52,55,59,67 Ten studies with analyzable data31,32,34,39,41,42,51,52,55,59 showed that the administration of PEG split-dose regimens yielded significantly greater proportions of patients with adequate preparations (OR, 2.60; 1.46;4.63).

NaP split-dose vs NaP day-before regimen. Six trials (1609 patients) were included in the comparison of NaP split-dose with day-before NaP intake. Four trials56,60,61,65 showed the administration of NaP split-dose regimens significantly increased adequate preparations compared with day-before regimens (OR, 2.51; 1.86;3.39) (Figure 3 and Table 1).

Table 1. Primary Outcome: Bowel Cleanliness

<table>
<thead>
<tr>
<th>Bowel cleanliness</th>
<th>Numbers of trialsa</th>
<th>ITT patients</th>
<th>OR (95% CI) or WMD (95% CI)</th>
<th>Heterogeneity</th>
<th>P value</th>
<th>I^2</th>
<th>P value Eggers</th>
<th>P value Beggs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split-dose vs day-before</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Split-dose of any product vs day-before of any product</td>
<td>32</td>
<td>8199</td>
<td>2.51 (1.86–3.39)</td>
<td>&lt;.01</td>
<td>84.8%</td>
<td>.51</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td>PEG split-dose vs PEG day-before</td>
<td>10</td>
<td>2923</td>
<td>2.60 (1.46–4.63)</td>
<td>&lt;.01</td>
<td>88.3%</td>
<td>.11</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>NaP split-dose vs NaP day-before</td>
<td>4</td>
<td>1018</td>
<td>9.34 (2.12–41.11)</td>
<td>&lt;.01</td>
<td>87.7%</td>
<td>.73</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>PICO split-dose vs PICO day-before</td>
<td>1</td>
<td>250</td>
<td>3.54 (1.95–6.45)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Split-dose vs another split-dose comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG split high-dose (≥3 L) vs PEG split low-dose (&lt;3 L)</td>
<td>6</td>
<td>1305</td>
<td>1.89 (1.01–3.46)</td>
<td>&lt;.01</td>
<td>76.7%</td>
<td>.45</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>PEG split vs NaP split</td>
<td>1</td>
<td>218</td>
<td>0.35 (0.15 to 0.85)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PEG split vs PICO split</td>
<td>1</td>
<td>89</td>
<td>6.32 (1.30–30.81)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PEG split vs OSS split</td>
<td>1</td>
<td>379</td>
<td>1.07 (0.50–2.29)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NaP split vs PICO split</td>
<td>1</td>
<td>372</td>
<td>1.15 (0.49–2.67)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Bolded values are statistically significant values.
CI, confidence interval.
aTrials with analyzable data.
included analyzable data, showing greater adequate preparations for NaP split-dose (OR, 9.34; 2.12; 41.11).

**PICO split-dose vs PICO day-before regimen.** Two trials, compared PICO split-dose vs day-before PICO (517 patients), with only 1 trial including analyzable data. PICO split-dose yielded a significantly greater proportion of adequate preparations (OR, 3.54; 1.95; 6.45).

**OSS split-dose vs OSS day-before regimen.** To our knowledge, no fully published trial has compared OSS split-dose with day-before OSS.

**Split-dose vs another split-dose regimen.** PEG split high-dose (≥3 L) vs PEG split low-dose (<3 L). Eight trials evaluated PEG split-dose in high- vs low-volume regimens (2165 patients), including 6 with analyzable data. PEG split high-dose yielded a greater proportion of patients with adequate preparations (OR, 1.89; 1.01; 3.46).

**PEG split-dose vs NaP split-dose regimen.** One trial of 218 patients comparing PEG vs NaP, with split-doses in both groups, showed no significant between-group differences.

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**Figure 2.** Cochrane risk bias tool.

**Figure 3.** Forest plot. Bowel cleanliness for split-dose of any regimen vs day-before.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>OR</th>
<th>95%-CI W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanner et al. 1990</td>
<td>18 54</td>
<td>38 48</td>
<td>0.13</td>
<td>[0.05; 0.32]</td>
</tr>
<tr>
<td>Paoluzi et al. 1993</td>
<td>51 80</td>
<td>45 80</td>
<td>1.37</td>
<td>[0.73; 2.58]</td>
</tr>
<tr>
<td>Kofts et al. 1993</td>
<td>27 34</td>
<td>37 79</td>
<td>4.38</td>
<td>[1.71; 11.22]</td>
</tr>
<tr>
<td>Marshall et al. 1993</td>
<td>60 70</td>
<td>68 73</td>
<td>0.64</td>
<td>[0.23; 1.78]</td>
</tr>
<tr>
<td>Cohen et al 1994</td>
<td>90 143</td>
<td>141 279</td>
<td>1.66</td>
<td>[1.10; 2.51]</td>
</tr>
<tr>
<td>Chia et al 1995</td>
<td>33 39</td>
<td>25 40</td>
<td>3.30</td>
<td>[1.12; 9.72]</td>
</tr>
<tr>
<td>Unal et al 1998</td>
<td>15 18</td>
<td>12 28</td>
<td>6.67</td>
<td>[1.57; 28.36]</td>
</tr>
<tr>
<td>Arezzo et al 2000</td>
<td>68 100</td>
<td>88 200</td>
<td>2.70</td>
<td>[1.63; 4.48]</td>
</tr>
<tr>
<td>Young et al 2000</td>
<td>131 169</td>
<td>86 154</td>
<td>2.73</td>
<td>[1.68; 4.41]</td>
</tr>
<tr>
<td>El Sayed et al 2003</td>
<td>75 91</td>
<td>66 90</td>
<td>2.53</td>
<td>[1.07; 4.25]</td>
</tr>
<tr>
<td>Tasci et al 2003</td>
<td>510 517</td>
<td>380 436</td>
<td>10.74</td>
<td>[4.84; 23.62]</td>
</tr>
<tr>
<td>Ell et al 2003</td>
<td>76 123</td>
<td>15 62</td>
<td>5.07</td>
<td>[2.55; 10.06]</td>
</tr>
<tr>
<td>Aoun et al 2005</td>
<td>52 68</td>
<td>41 73</td>
<td>2.54</td>
<td>[1.23; 5.24]</td>
</tr>
<tr>
<td>Hwang et al 2005</td>
<td>30 40</td>
<td>33 40</td>
<td>0.64</td>
<td>[0.22; 1.68]</td>
</tr>
<tr>
<td>Frauen-Blanco et al 2006</td>
<td>36 45</td>
<td>15 89</td>
<td>19.73</td>
<td>[7.88; 49.39]</td>
</tr>
<tr>
<td>Wrubl et al 2007</td>
<td>144 171</td>
<td>50 68</td>
<td>1.92</td>
<td>[0.98; 3.76]</td>
</tr>
<tr>
<td>Johansen et al 2007</td>
<td>184 207</td>
<td>169 208</td>
<td>1.85</td>
<td>[1.00; 3.22]</td>
</tr>
<tr>
<td>Abdul-Baki et al 2008</td>
<td>177 199</td>
<td>78 183</td>
<td>10.83</td>
<td>[3.7; 18.42]</td>
</tr>
<tr>
<td>Worthington et al 2008</td>
<td>27 32</td>
<td>24 33</td>
<td>2.02</td>
<td>[0.60; 6.68]</td>
</tr>
<tr>
<td>Chen TA et al 2009</td>
<td>103 140</td>
<td>35 136</td>
<td>8.03</td>
<td>[4.00; 13.75]</td>
</tr>
<tr>
<td>Malik et al 2009</td>
<td>74 80</td>
<td>31 41</td>
<td>3.98</td>
<td>[1.33; 11.90]</td>
</tr>
<tr>
<td>Corporaal et al 2010</td>
<td>209 220</td>
<td>77 87</td>
<td>2.47</td>
<td>[1.01; 6.04]</td>
</tr>
<tr>
<td>Cohen et al 2010</td>
<td>48 55</td>
<td>49 55</td>
<td>0.84</td>
<td>[0.26; 2.68]</td>
</tr>
<tr>
<td>Park SS et al 2010</td>
<td>61 95</td>
<td>40 95</td>
<td>2.47</td>
<td>[1.37; 4.43]</td>
</tr>
<tr>
<td>Marmo et al 2010</td>
<td>327 448</td>
<td>186 447</td>
<td>3.79</td>
<td>[2.86; 5.02]</td>
</tr>
<tr>
<td>Rex et al 2010</td>
<td>62 68</td>
<td>60 68</td>
<td>1.38</td>
<td>[0.45; 4.21]</td>
</tr>
<tr>
<td>Samarasekara et al 2012</td>
<td>83 105</td>
<td>30 117</td>
<td>10.94</td>
<td>[5.84; 20.48]</td>
</tr>
<tr>
<td>Manno et al 2012</td>
<td>160 168</td>
<td>156 168</td>
<td>1.54</td>
<td>[0.61; 3.67]</td>
</tr>
<tr>
<td>Fleming et al 2012</td>
<td>107 127</td>
<td>74 123</td>
<td>3.54</td>
<td>[1.95; 6.45]</td>
</tr>
<tr>
<td>Cesare et al 2013</td>
<td>24 51</td>
<td>32 52</td>
<td>0.56</td>
<td>[0.25; 1.22]</td>
</tr>
<tr>
<td>Rex et al 2013</td>
<td>256 305</td>
<td>221 298</td>
<td>1.82</td>
<td>[1.22; 2.72]</td>
</tr>
<tr>
<td>Voilosu et al 2013</td>
<td>63 94</td>
<td>49 87</td>
<td>1.58</td>
<td>[0.86; 2.68]</td>
</tr>
</tbody>
</table>

**Random effects model**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95%-CI W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.51</td>
<td>[1.86; 3.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: I^2=84.8%, t^2=0.5937, P<.0001
differences in the mean total Ottawa scale scores (WMD, 0.35; -0.15; 0.85).

**PEG split-dose vs PICO split-dose regimen.** A comparison of PEG split-dose with PICO with mannitol split-dose (89 patients) favored the former group with regard to adequate preparation rates $^{73}$ (OR, 6.32; 1.30; 30.81).

**PEG split-dose vs OSS split-dose regimen.** One trial $^{68}$ comparing split-dose PEG vs split-dose OSS (379 patients) yielded no between-group differences in bowel cleanliness (OR, 1.07; 0.50; 2.29).

**NaP split-dose vs PICO split-dose regimen.** One trial $^{74}$ compared NaP with PICO, both in split-dose (372 patients), with no differences in bowel cleanliness (OR, 1.15; 0.49; 2.67).

To our knowledge, no published trials have compared split-dose NaP with OSS split-dose, or PICO split-dose vs OSS split-dose.

A summary of all comparisons of bowel cleanliness trials is listed in Table 1.

**Secondary Outcomes: Willingness to Repeat**

Information on a patient’s willingness-to-repeat the same preparation was available in 14 trials for split-dose vs day-before regimens (4377 patients). $^{32,34,35,38-40,42,46,48,50,51,55,58,60}$ This outcome was increased significantly in patients receiving split-dose of any regimen (OR, 1.90; 1.05; 3.46).

Willingness to repeat was decreased significantly for PEG split high-volume ($\geq 3$ L) compared with PEG split low-volume (<3 L) (OR, 0.20; 0.09; 0.45) (3 trials, 661 patients $^{25,69,76}$) (Table 2).

**Secondary Outcomes: Polyp or Adenoma Detection, Side Effects or Complications, and Additional Time Required to Resume Daily Activities**

No significant between-regimen differences existed with regard to the outcomes of polyp or adenoma detection with only 2 trials included. Other side effects and additional time required to resume daily activities are available in Appendix 2.

**Sensitivity Analyses**

Sensitivity analyses results were concordant with the main analysis, with some trends not achieving significant differences, whereas significant heterogeneity remained except in small subgroups (details in Appendix 2). The observed summary odds ratio for “excellent” or “optimal” bowel cleanliness increased from having used a cut-off for “excellent and good” from (n = 32) 2.51 (1.86-3.39) to (n = 21) 2.69 (1.96-3.68).

Additional secondary outcome results are available in Appendix 2.

**Meta-regression Analysis**

By using meta-regression, no significant predictors were noted among the independent variables of year of publication after 2004 (OR, 0.96; 0.36;2.54), trial conducted in North America (OR, 0.64; 0.24;1.71), and day-before liquid diet ingestion (OR, 1.33; 0.51;3.47).

**Discussion**

The aim of the current systematic review was to summarize existing evidence to inform recommendations by the MSTF group with regard to certain targeted statements on colonic preparation regimens. They include data addressing split-dose for bowel cleanliness and willingness to repeat. The principal conclusions confirm that use of split-dose regimens results in greater proportions of patients with adequate preparations (OR, 2.51; 1.86;3.39) as outlined in Table 3. The superiority of split-dose may relate to the shortened interval of time between the last intake of preparation product and the colonoscopy. $^{78}$ Most of the included trials initiated the preparation at 5:00 or 6:00 AM. Supplementary Table 1 provides the information broken down according to dosage regimen, time of colonoscopy, and runway time. However, in the absence of demographic data specifically assessing patients scheduled for early

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**Table 2. Secondary Outcome: Willingness-to-Repeat**

<table>
<thead>
<tr>
<th>Willingness-to-repeat</th>
<th>Numbers of trials</th>
<th>OR (95% CI)</th>
<th>Heterogeneity</th>
<th>$I^2$</th>
<th>P value Eggers</th>
<th>P value Beggs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split-dose vs day-before comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Split-dose of any vs day-before of any product</td>
<td>14</td>
<td>4377</td>
<td><strong>1.90 (1.05–3.46)</strong></td>
<td>&lt;.01</td>
<td>92.8%</td>
<td>.04</td>
</tr>
<tr>
<td>PEG split-dose vs PEG day-before</td>
<td>7</td>
<td>1146</td>
<td>0.97 (0.40–2.37)</td>
<td>&lt;.01</td>
<td>89.3%</td>
<td>.07</td>
</tr>
<tr>
<td>Split-dose vs another split-dose comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG split high-dose ($\geq 3$ L) vs PEG split low-dose (&lt;3 L)</td>
<td>3</td>
<td>661</td>
<td><strong>0.20 (0.09–0.45)</strong></td>
<td>.13</td>
<td>51.4%</td>
<td>.30</td>
</tr>
<tr>
<td>PEG split vs NaP split</td>
<td>1</td>
<td>212</td>
<td>0.64 (0.37–1.12)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PEG split vs PICO split</td>
<td>1</td>
<td>89</td>
<td>1.91 (0.63–5.81)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NOTE. Bolded values are statistically significant values.
CI, confidence interval.
*Trials with analyzable data.
colonoscopy, we cannot address any possible selection bias or lack of generalizability of the summary findings.

Marked statistical heterogeneity was noted, however, suggesting disparity in findings, and justifying the many preplanned sensitivity analyses and meta-regression in search of possible explanations. Variations in clinical protocols (such as differing products and their volumes, use of adjuvants, associated diets), as well as varying definitions in both split-dose regimens and the main outcome measures of bowel cleanliness exist, which can explain this observation, in addition to disparities in statistical findings. With few exceptions, statistical heterogeneity remained despite multiple sensitivity analyses according to the colon preparation scale used, whether a PP or ITT approach was adopted, varying the cleanliness definition, year of publication, country, or type of diet.

Adjuvants were distributed with no marked differences between the different comparisons (data available upon request). Magnesium citrate is known to be used frequently in the United States, but mostly in combination with a product, we therefore considered it as an adjuvant for the analyses. Importantly, the magnitude of improvement in the proportion of adequate preparations with split PICO was similar to that noted with split PEG regimens, suggesting the importance of the choice of a split-dose regimen.

PEG is considered a bowel cleansing product associated with less electrolyte imbalances. More recent alternatives to PEG have included PICO and oral NaP-based preparations. PICO is known to interact with medications that can affect electrolyte balance. OSS omits the phosphates responsible for significant fluid and electrolyte imbalances. Both PICO and OSS can cause symptoms of dehydration, leading to the need for additional intake of fluids by the patient. All products are contraindicated in specific conditions.

Although we included data on NaP preparations, concerns of nephrotoxicity have motivated a Food and Drug Administration warning and resulted in rarer use of this product.

PICO was approved in the United States in 2012. Four trials assessed PICO split-dose regimens: 2 trials showed the superiority of PICO split-dose vs day-before PEG 2 L or a PICO day-before regimen. Another trial showed no difference compared with split NaP, and the fourth trial found significantly less adequate preparations for split-dose PICO compared with split-PEG 4 L. Two additional trials assessed other PICO regimens: a day-before PICO regimen was not different from a PEG 2 L split preparation, whereas the last trial showed superiority of split-PEG 4 L over day-before PICO, but only in per-protocol analysis. We favored ITT analysis, when analyzable, because of the relationship between adherence to the preparation protocol and bowel cleanliness, with its generalizability to a real-life setting.

Two trials assessed OSS split-dose regimens (approved in the United States in 2010): Di Palma et al showed no differences in bowel cleanliness between split-dose OSS and split-dose PEG 2 L, whereas Rex et al found split-dose OSS to be superior to day-before PEG 4 L, but only in PP analysis.

Taken together with the NaP split-dose trials (Table 1), the aforementioned summary results in the published literature suggest that split-dose administration impacts more meaningfully on bowel cleanliness than its actual choice of compound. We identified only 4 head-to-head split-dose trials: 3 showed no differences, but a PEG 4 L split-dose resulted in greater adequate bowel preparation rates than a PICO split-dose regimen (with mannitol) (n = 89 patients; OR, 6.32; 1.30;30.81).33

As for the choice of PEG split-dose volumes, 3 L or more yielded higher rates of adequate preparations than lesser-volume regimens, however, with a lower confidence interval narrowly greater than 1 (OR, 1.89; 1.01;3.46); moreover, the difference was not significant in PP analysis, showed significant statistical heterogeneity, and the use of adjuvants and their nature varied greatly across studies. This is why

Table 3. Outcomes for Split-Dose of any Product vs Day-Before of any Product

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of trials* (number of included patients)</th>
<th>OR (95% CI); heterogeneity (P value, I²)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: bowel cleanliness (excellent/good)</td>
<td>32 (8199)</td>
<td>2.51 (1.86–3.39); P &lt; .01, 84.8%</td>
<td>Split-dose regimens yield the highest quality of colon cleansing across all types of colonic preparations</td>
</tr>
<tr>
<td>Secondary outcome: willingness-to-repeat</td>
<td>14 (4377)</td>
<td>1.90 (1.05–3.46); P &lt; .01, 92.8%</td>
<td>Willingness-to-repeat is enhanced by the use of split-dose vs day-before regimens of any product</td>
</tr>
<tr>
<td>Secondary outcome: polyp detection rate</td>
<td>2 (159)</td>
<td>0.93 (0.41–2.13); P &lt; .52, 0.0%</td>
<td>More trials are required to conclude on procedural outcomes</td>
</tr>
<tr>
<td>Secondary outcome: adenoma detection rate</td>
<td>2 (213)</td>
<td>1.52 (0.69–3.32); P &lt; .19, 42.2%</td>
<td></td>
</tr>
<tr>
<td>Secondary outcome: side effects and resumption of daily activities</td>
<td>0 to 24 (6434)</td>
<td>See Appendix 2</td>
<td>More uniform definitions across studies are required to conclude on side effects and resumption of daily activities</td>
</tr>
</tbody>
</table>

Cl, confidence interval.

*Trials with analyzable data.
we suggest that additional head-to-head data are needed to conclude more confidently on this issue. Willingness-to-repeat, however, strongly favored low-volume split-dose preparations (OR, 0.20; 0.09;0.45).

The choice of willingness-to-repeat as a secondary outcome reflects a pragmatic clinical argument because patient tolerance in part determines bowel cleanliness (the adopted primary outcome). The only significant finding in willingness-to-repeat, other than the aforementioned superiority of PEG low-volume vs PEG high-volume split-dose preparation, was in the comparison of split-dose vs day-before regimens of any product.

Patient symptoms related to the preparation were reported inconsistently and in a highly variable fashion, forcing an empiric regrouping of symptoms for the analysis. Statistical heterogeneity varied according to symptom subgroup. Nausea or vomiting was reported more often with NaP split-dose than day-before NaP (2 trials), and less often with PEG split-dose than with NaP split-dose (1 trial). Chills were significantly less frequent with split-dose compared with day-before for all products. The only other significant symptom difference was a greater incidence of perianal irritation with PEG split-dose vs PICO split-dose (1 trial). Electrolytic imbalances were reported inconsistently and could not be analyzed (Appendix 2).

The superiority of split-dose regimens in bowel cleansing was reported by 4 previous meta-analyses. Belsey et al did not address preparation cleanliness as a primary outcome in a recent meta-analysis. Kilgore et al compared PEG 4 L split-dose with day-before or same-day PEG 4 L, excluding any trials with adjuvants. Only 4 trials with analyzable data were included; bowel cleanliness was increased by PEG 4 L split-dose (OR, 3.70; 2.79;4.91), as was willingness-to-repeat (OR, 1.76; 1.06;2.91), although side effects did not differ between groups. Enestvedt et al compared PEG 4 L split-dose with any other type of preparation including some other products using split-doses and/or adjuvants. With 9 abstracts or published trials included, PEG 4 L split-doses yielded a greater proportion of excellent or good preparations compared with any other regimen (OR, 3.46; 2.45;4.89). Willingness-to-repeat and side effects did not differ. The latest meta-analysis from Bucci et al reported similar conclusions for the split-doses vs any non-split-dose regimens with a rate difference of 0.22 (0.16;0.27). Although well-constructed, the investigators included only 29 trials, moreover, the analyses were reported as rate differences, a suboptimal summary statistic. The comparison of split-dose NaP vs non-split-dose NaP (only 4 trials reported) by Bucci et al included the OSS study from Rex et al which we considered separately as a novel product. The interesting comparisons assessed by Bucci et al in contrast to those outlined in the current meta-analysis, varied at the same time product and split vs non-split regimens. This design makes it more difficult to draw broad pertinent clinical conclusions, especially in the absence of additional analyses assessing willingness to repeat, procedural information, and side effects. Split-dose preparations recently were endorsed by the US MSTF and the European Society for Gastrointestinal Endoscopy, who acknowledged that further research is needed to better identify optimal approaches among these regimens. A separate series of meta-analyses, also in the context of the MSTF recommendations on bowel preparations, is being completed to assess the use of adjuvants as well as the adoption of specific dietary recommendations, which is why we have not focused on these in this article.

Conclusions

Split-dose regimens yield the highest quality of colon cleansing across all types of colonic preparations. Willingness-to-repeat is enhanced by the use of split-dose vs day-before regimens of any product, and by the adoption of low- vs high-volume PEG split-dose regimens. More uniform definitions across studies are required to conclude on other secondary outcomes such as side effects, polyp and adenoma detection, and resumption of daily activities. Future research must focus on comparing split-PEG dosing of large and low-volumes, split-dose vs same-day preparations, and direct evaluations of PEG-based vs PICO and OSS preparations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.04.004.

References


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Conflicts of interest
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