TECHNICAL REVIEW

Optimal bowel cleansing for colonoscopy: split the dose! A series of meta-analyses of controlled studies

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Background: Colonoscopy is considered the criterion standard for detecting colorectal cancer; adequate preparation is crucial for an effective colonoscopy, but definitive data on the optimal preparation are lacking.

Objective: Our aim was to assess the efficacy of split-dose versus non-split–dose preparations, the rate of adequate preparation according to type and dose of laxatives, the role of "runway time" (the interval time between the last drink of purgative and the beginning of colonoscopy), and to evaluate compliance as an additive risk factor for colon cleansing.

Design: A series of meta-analyses of controlled studies.

Setting: Randomized clinical trial of split dose regimen versus entire dose taken on the day preceding colonoscopy.

Patients: Published trials (1960-2013) comparing split-dose versus non-split–dose preparations in adults undergoing colonoscopy were selected by using MEDLINE, the Cochrane Central Register of Controlled Trials, clinicaltrial.gov, ISI Web of Science, and Scopus.

Interventions: Colonoscopy.

Main Outcome Measurements: Rate difference of the degree of colon cleansing between split dose and whole dose was the primary measure of treatment effect.

Results: We included 29 studies. Overall, an adequate preparation was obtained in 85% of patients in the split-dose group and in 63% of the non-split–dose group (rate difference 22%). The heterogeneity was caused by 5 factors: the runway time (the longer, the worse the cleansing), type of diet, male sex, use of polyethylene glycol 4 L, and the Jadad score. Compliance was significantly higher in the split-dose group.

Limitations: Average quality of the included studies and publication bias.

Conclusion: We provided further evidence of the superiority of a split-dose regimen over a non-split–dose regimen and showed that, regardless of type and dose, the superiority of split-dose regimens remains valid if the "golden 5 hours" rule is preserved. (Gastrointest Endosc 2014;80:566-76.)

Colonoscopy is considered the criterion standard in detecting colorectal cancer and, more importantly, its precursors such as polypoid or flat lesions. The first step toward a high-quality colonoscopy is a clean colon. Indeed, inadequate cleansing can result in missed lesions, aborted procedures, increased procedure time and, potentially, adverse events, together with reduced patient comfort.[1,2] Commercially available bowel cleansing preparations contain osmotic components (sodium phosphate [NaP]), isotonic solution (polyethylene glycol [PEG]), or irritant laxatives (sodium picosulphate). In literature, many studies show that all those laxatives are associated with good colon cleansing, but there is no clear-cut superiority or a specific dosing regimen that is better than another. Also, alternative dosages (eg, PEG 2 L or low volume [PEG-low]) or different regimens (splitting the dose, in which the laxative is split into 2 half doses between the day before and the day of the examination or same day

Abbreviations: ESGE, European Society of Gastrointestinal Endosocopy; G/E, good and/or excellent; NaP, sodium phosphate; PEG, polyethylene glycol; PEG-high, PEG high volume (4 L); PEG-low, PEG low volume (2 L); RD, rate difference.

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regimen, suggested for afternoon colonoscopies) were tested recently, with an apparent increase in efficacy and patient compliance, but definitive data are still missing.[3]

Objectives

The primary endpoints were to compare the efficacy in terms of colon cleansing of the split-dose regimen compared with the non-split–dose regimen, regardless of the type and doses of laxative and the efficacy of different laxatives in patients undergoing colonoscopy. Secondary endpoints were (1) to compare the rate of good and/or excellent (G/E) bowel preparation in different subgroups of patients according to the type and dosage of the laxative, (2) to assess the role of "runway-time" (the interval time between the last drink of laxative and the beginning of colonoscopy), and (3) to evaluate the rate of compliance as an additive risk factor for colon cleansing.

METHODS

Study selection

A systematic review of published articles (1960-2013) comparing split-dose versus non-split–dose regimens in adults undergoing colonoscopy by using MEDLINE, the Cochrane Controlled Trials Register, clinicaltrial.gov, ISI Web of Science, and Scopus was performed. Search terms included "bowel," "preparation," "colon," "cleaning," and "colonoscopy." Studies were identified also by scanning reference lists of articles. No limits were applied for language, and foreign articles were translated, when possible. Abstracts were screened separately by 2 authors and selected if the following inclusion criteria were fulfilled: (1) randomized clinical trials, (2) split-dose versus non-split–dose regimens, and (3) patient age >18 years. Abstracts were excluded if they did not fulfill the inclusion criteria and/or if there was a special interest in a subgroup of patients (older, inpatients, pediatrics, etc). Then the full texts of selected articles were retrieved in extenso. A predefined data extraction sheet (containing a pilot test on 10 randomly selected included studies performed in advance) was used. Two authors extracted independently the following data from each article: patient characteristics (age; sex; diet before preparation; time of colonoscopy; use of cathartics; compliance to the laxative; type, dose, and regimen of preparation; scale used to evaluate colon cleansing; degree of colon cleansing (grouping; excellent-good vs poor-fair); study quality indicators for the Jadad score[4] and analysis type (intention to treat or per protocol). If one or more variables was not immediately inferable, principal investigators were contacted by e-mail. If primary outcomes were not available, the study was then excluded. The Jadad score was rated for each trial by 2 authors, and then the final ratings were determined by consensus.

Data synthesis

The rate difference (RD) of the degree of colon cleansing between split dose and whole dose was the primary measure of treatment effect. The meta-analyses were performed by computing RD by using a random-effects model, if heterogeneity was present. Quantitative analyses were performed on an intention-to-treat basis. Absolute rate of colon cleansing for split-dose and non-split–dose regimens, RD between them and 95% confidence intervals for each treatment arm, and pooled effect estimated were calculated.

Measures of treatment effect

Analysis was carried out for all patients undergoing split-dose versus non-split–dose regimens (overall analysis) for colonoscopy and according to specific type of laxative comparisons (subgroup analysis). The second analysis was realized by estimating the difference in colon cleansing degree between patients in the split-dose and in the non-split–dose groups.

Assessment of heterogeneity

To explore the heterogeneity, we specified the following hypotheses before conducting the analysis. We hypothesized that effect size may differ according to the methodologic quality of the studies, to the type of purge, to the time elapsed between the end of purge intake and the beginning of colonoscopy, the type of diet before laxative use, patient compliance, frequency of male sex, the scale used to evaluate colon cleansing, and the type of analysis performed (intention to treat vs per protocol).

Assessment of biases

We assessed the possibility of publication bias by evaluating a funnel plot of the trial effect rate for asymmetry. We conducted an Egger-Hardbord regression test as a formal predefined statistical test for publication bias, and we conducted the contour-enhanced funnel plots to aid in interpreting the funnel plot.

Subgroup analysis

A subgroup analysis was planned to test the secondary endpoints among groups of patients who took different laxatives. We tested for heterogeneity as described for the overall effect and calculated confidence intervals and *P* values for differences between the effect measure parameters for different subpopulations.

Sensitivity analysis

Sensitivity analyses were prespecified. The treatment effects were examined according to quality components (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment). Appendix 1 (available online at www.giejournal.org) extensively describes the statistical methods applied.