A Randomized, Controlled, Double-blind Trial of The Adjunct Use of Clebopride in Polyethylene Glycol Electrolyte (PEG) Solution for Colonoscopy Preparation

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ABSTRACT

Aim: *to study the benefit of Clebopride as an adjuvant in polyethylene glycol electrolyte (PEG) solution for colonoscopy preparation.*

Methods: *eighty one adult patients who underwent colonoscopy examination were recruited in this randomized double blind controlled study. First group received PEG and placebo, whereas second group received PEG and Clebopride. Two litres of PEG was taken at night before colonoscopy. The acceptability and tolerability of bowel preparation were assessed through interview method. The efficacy of bowel preparation was assessed using Aronchick's Criteria.*

Results: *in terms of acceptability, 64 patients (31 patients from placebo group* vs *33 patients from Clebopride group) were able to drink two litres of PEG solution. Sixty patients (29 patients from placebo group and 31 patients from Clebopride group) were willing to accept PEG solution for their next bowel preparation. On the term of tolerability, nausea, abdominal distension, and borborygmus were more frequent in the placebo group (34.2%* vs *27.9%; 44.7%* vs *32.6%; 26.3%* vs *4.6% respectively). However, only the difference at the incidence of borborygmus that was statistically significant (p <0 .05). On the terms of efficacy, both groups showed a comparable bowel preparation quality with 88.4% of bowel p reparation in Clebopride group and 81.6% of bowel preparation in placebo group were optimal (*p = *0.585).*

Conclusion: *the adjunct use of Clebopride in PEG solution for colonoscopy preparations tends to increase the acceptability, tolerability, and efficacy. The presence of borborygmus was significantly lower in the Clebopride group.*

Key words: *Clebopride, PEG, bowel preparation, Aronchick's criteria.*

INTRODUCTION

The numbers of large bowel disease are increasing year by year. Consequently, there is growing importance of the colonoscopy procedures. Moreover, widespread use of colonoscopy has been proposed for colorectal cancer screening. Colonoscopy requires thorough bowel preparation for safe and effective completion of the procedure. In fact, diagnostic accuracy and therapeutic safety of colonoscopy depend on the quality of the bowel preparation.[1-5]

The commonly used conventional pre-treatment for removing intestinal content is food restriction with a low residue diet followed by administration of several purgatives and/or enemas. This method is ineffective, painful, and unsafe as residue frequently remains in the colon. For the past decade, PEG solution has been the preferred bowel-cleansing regimen before diagnostic and therapeutic colonoscopy procedures on the colon and rectum. Nonetheless, the large volume of PEG that has to be consumed becomes its own limitation. Low-volume PEG solutions were developed in an attempt to improve patient tolerance. Clebopride, a D-2 dopamine antagonist with antiemetic and prokinetic properties, can improve the bowel cleansing efficacy.[6,7] Clebopride stimulates peripheral 5-HT4 receptors and shortens intestinal transit time.[8] However, the efficacy and tolerability of PEG with or without Clebopride have not been investigated.

Based on that, we conduct a prospective, randomized, controlled, double-blinded study to evaluate the acceptability, tolerability, and efficacy of Clebopride as an adjuvant in PEG solution for colonoscopy preparation.

METHODS

Selection of Patients

From June to December 2008, all patients aged 18 to 70 years that were referred for colonoscopy at Cipto Mangunkusumo Hospital were considered and approached for consent by their gastroenterologists. Patients were excluded if they had renal failure, unstable angina, acute coronary syndrome/congestive heart failure, ascites, megacolon, bowel obstruction, or other comorbidities that might prevent colonoscopy. Patients were also excluded if they had a previous partial or subtotal colectomy, or if the colonoscopy was performed for the evaluation of diarrhea.[9] Patients were divided into two groups using simple randomization. First group took PEG and placebo, whereas second group took PEG and Clebopride. Investigators and colonoscopists were blinded to group allocation. This study was reviewed and approved by the ethics committee of Faculty of Medicine University of Indonesia, who approved the protocol.

Intervention and Measurements

PEG administration was started at 12 hours before the colonoscopy procedure. All patients were instructed to drink PEG solution until the total amount of two litres or less if their stools had become pale yellow or almost transparent watery solution before the total amount was indigested. Solid food was allowed until one hour prior to PEG administration. Afterward, patients were only allowed to take mineral water. Clebopride (0.5 mg) and placebo were administered three times and given one day before colonoscopy.

Before undergoing colonoscopy procedure, patients were interviewed by an independent investigator to assess their acceptability and tolerability toward the bowel preparation. On the term of acceptability, patients were assessed using two parameters that were the ability to drink the total amount of two litres PEG solution and the willingness to accept re-examination with the same drug. On the terms of tolerability, patients were asked for any adverse events related to the bowel preparation such as bloating, nausea, vomiting, and abdominal cramps. Patients were instructed not to discuss their bowel preparation with their gastroenterologist. A procedure was established to address patients' concerns and issues of safety, without interfering with the gastroenterologist blinding system.

The efficacy of bowel preparation was assessed using the Aronchick's criteria (**Table 1**). The participating endoscopists were trained to use the Aronchick's criteria in order to achieve good level of agreement.[10]

Table 1. Aronchick's criteria for the efficacy of bowel preparation assessment

Observation	Aronchick's criteria
• Small volume of clear liquid • Greater than 95% of surface seen	**EXCELLENT**
• Large volume of clear liquid covering 5% to 25% of the surface • Greater than 90% of surface seen	**GOOD**
• Some semisolid stool that could be suctioned or washed away • Greater than 90% of surface seen	**FAIR**
• Some semisolid stool that could not be suctioned or washed away • Less than 90% of surface seen	**POOR**
• Repeat preparation • Colonoscopy needed	**INADEQUATE**

The final assessment of bowel preparation was divided into two categories that were optimal and non-optimal. The bowel preparation considered fair, good, or excellent based on Aronchick's criteria were assessed as optimal bowel preparation, while others as non-optimal. Colonoscopy was performed on standard procedure. The endoscopists rated the bowel-preparation efficacy during the procedure and recorded the results on a separate standardized form.

Data Analysis

On the basis of data from previous study by Brady CE 3rd *et al.*[11] a sample size of 39 per arm for the primary end point was estimated to give an 80% power at a two-sided alpha of 0.05. Thus, the total sample size required will be 86 patients (43 per arm) to accommodate an additional 10% drop out. Analysis was done using the STATA version 9.0 software (STATA Corporation, TX, USA). The proportions in 2 x 2 contingency tables were compared by using the Chi square test, with the Yates correction for continuity. A p value of less than 0.05 was considered significant.

RESULTS

Baseline Characteristics of Patients

Of the 86 randomized patients, 81 patients completed the study. Five patients were excluded because of suspected bowel obstruction. The baseline characteristics are presented in **Table 2**. The most common reasons for colonoscopy were bleeding (45.9% in placebo group *vs* 45.2% in Clebopride group) and screening (21.6% in placebo group *vs* 23.8% in Clebopride group).

Table 2. Baseline characteristics of patients

Characteristics	Preparation group	
	PEG + Placebo	PEG + Clebopride
Age, N (mean), y	38 (43.76)	43 (45.88)
Gender, n (%)		
Men	20 (52.6%)	16 (37.2%)
Women	18 (47.4%)	27 (62.8%)
Indications, %		
Bleeding	45.9	45.2
Screening	21.6	23.8
Chronic diarrhea	16.2	19.0
Other	16.2	11.9

Acceptability of Bowel Preparation

The acceptability of bowel preparation was presented in **Table 3**. Concerning the volume, 64 patients (79%) that consisted of 31 patients from placebo group *vs* 33 patients from Clebopride group were able to drink two litres of PEG solution. Forty six patients (56.8%) stated that they could have drunk more; 26 patients (32.1%) stated that it was barely drinkable; seven patients (8.6%) stated that it was drinkable although it was a little-bit too much; and only two patients (2.5%) stated that it was too much.

Table 3. Acceptability of bowel preparation

	Preparation group n (%)		*p* value
	PEG + Placebo	PEG + Clebopride	
The ability to drink two litres PEG solution	31 (81.6%)	33 (76.7%)	0.795
The willingness to accept re-examination with same drug	29 (76.3%)	31 (72.1%)	0.858

Sixty patients (74.1%), 29 patients from placebo group and 31 patients from Clebopride group, were willing to accept PEG solution for their next bowel preparation. Patients' acceptability was comparable between these two groups.

Tolerability of Bowel Preparation

The tolerability of bowel preparation was presented in **Table 4**. Nausea, retching, vomiting, abdominal pain, abdominal distension , borborygmus, and hemorrhoid pain were the adverse events reported. Of all the adverse events, nausea and abdominal distension were more frequently found in the placebo than in Clebopride group, but they were not statistically significant (p = 0.710 and p = 0.370, respectively). On the other hand, borborygmus was significantly less frequent in the Clebopride group (p = 0.015).

Table 4. Tolerability of bowel preparation

	Preparation group n (%)		*p* value
	PEG + Placebo	PEG + Clebopride	
Nausea	13 (34.2%)	12 (27.9%)	0.710
Retching	2 (5.3%)	3 (7.0%)	1.000
Vomiting	3 (7.9%)	4 (9.3%)	1.000
Abdominal pain	8 (21.1%)	10 (23.3%)	1.000
Abdominal distension	17 (44.7%)	14 (32.6%)	0.370
Borborygmus	10 (26.3%)	2 (4.7%)	0.015
Hemorrhoid pain	15 (39.5%)	19 (44.2%)	0.839

Efficacy of Bowel Preparation

The efficacy of bowel preparation was presented in **Figure 1**. As much as 88.4% of bowel preparation in Clebopride group was optimal, while only 81.6% of bowel preparation in placebo group was optimal. Both placebo and Clebopride groups showed a comparable overall assessment of bowel preparation (*p* = 0.585).

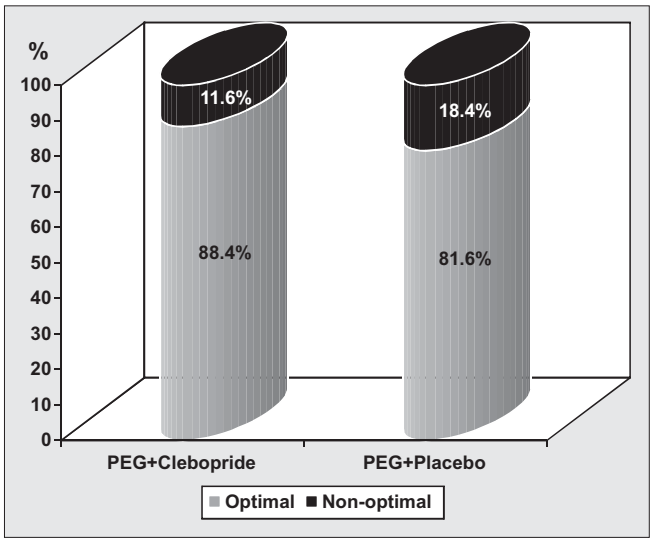

Figure 1. The efficacy of bowel preparation

DISCUSSION

Bowel preparations are generally regarded as unpleasant procedure by patients. It is not uncommon for patients to state that the preparation is worse than the actual colonoscopy. As the result, various products and additives have been studied in order to obtain a shorter preparation interval with smaller volume of purgative and prokinetic agent.

Many studies regarding PEG solution have concluded that PEG is more effective and better tolerated than the combination of diet and cathartic regimens, high-volume balanced electrolyte solutions, and mannitol-based

solutions.[12-15] Although PEG is generally well tolerated, five to 15 percent patients who receive PEG do not complete the preparation because of poor palatability and/or large volume.[16]

The authors intended to study the adjunct use of Clebopride in PGE solution for colonoscopy preparation. Clebopride, a D-2 dopamine antagonist and peripheral 5-HT4 receptor agonist, has antiemetic and prokinetic properties. Clebopride can improve bowel cleansing efficacy and shorten intestinal transit time. Clebopride up to one milligram is considered safe. Clebopride may have torsadogenic potency in supratherapeutic concentration.[17]

This study showed that patients' acceptability was comparable between Clebopride and placebo groups ($p > 0.05$). On the subject of tolerability, clebopride reduced the presence of nausea, abdominal distension, and borborygmus. This was consistent with other study that stated metoclopramide, a D-2 dopamine antagonist, could reduce nausea and bloating.[17] However, only the difference at the presence of borborygmus that was statistically significant ($p = 0.015$).

The efficacy of bowel preparation assessed with Aronchick's criteria was found comparable between placebo and Clebopride groups ($p = 0.585$). This was consistent with other studies that found no statistically significant differences between the strategies for bowel preparation.[9,11,18-20]

CONCLUSION

In general, this study demonstrates that PEG solution is effective for bowel preparation. Clebopride tends to increase the acceptability, tolerability, and efficacy of bowel preparation using PEG although most of them were not statistically significant. Regarding tolerability, the adverse events of borborygmus was significantly less frequent in the Clebopride group.

REFERENCES

1. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. NEJM. 2006;355:1863–72.
2. Piscatelli N, Hyman N, Osler T. Localizing colorectal cancer by colonoscopy. Arch Surg. 2005;140:932-5.
3. Sonnenberg A, Delcò F. Cost-effectiveness of a single colonoscopy in screening for colorectal cancer. Arch Intern Med. 2002;162:163–8.
4. Heitman SJ, Manns BJ, Hilsden RJ, Fong A, Dean S, Romagnuolo J. Cost-effectiveness of computerized tomographic colonography versus colonoscopy for colorectal cancer screening. CMAJ. 2005;173(8):877-81.
5. American Society for Gastrointestinal Endoscopy. A consensus document on bowel preparation before colonoscopy. Gastrointest Endosc. 2006;63(7):894-909.
6. American Society for Gastrointestinal Endoscopy. Colonoscopy preparation. Gastrointest Endosc. 2009;69(7): 1201-9.
7. Lenz HJ , Schuler U, Hicking W, Ehninger G. Phase 1-trial of clebopride, a new antiemetic, in chemotherapy-induced nausea and vomiting. EurJ Clin Pharmacol. 1990;38:525.
8. Brunton LL, Parker KL. Treatment of disorders of bowel motility and water flux; antiemetics; agents used in biliary and pancreatic disease. Goodman and Gilman's: Manual of pharmacology and therapeutics. New York: Mc Graw Hill; 2008. p 633-5.
9. Rostom A, Jolicoeur E, Dube C, Gregoire S, Patel D, Saloojee N, et al. A randomized prospective trial comparing different regimens of oral sodium phosphate and polyethylene glycol–based lavage solution in the preparation of patients for colonoscopy. Gastrointest Endosc. 2006;64:544-52.
10. Aronchick CA, Lipshutz WH, Wright SH, Dufrayne F, Bergman G. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. Gastrointest Endosc. 2000; 52:346–52.
11. Brady CE III, DiPalma JA, Pierson WP. Golytely lavage—is metoclopramide necessary? Am J Gastroenterol. 1985; 80(3):180-4.
12. Chan CH, Diner WC, Fontenot E, et al. Randomized single-blind clinical trial of a rapid colonic lavage solution versus standard preparation for barium enema and colonoscopy. Gastrointest Radiol. 1985;10:378-82.
13. Burke DA, Mannin AP, Murphy L, et al. Oral bowel lavage preparation for colonoscopy. Postgrad Med J. 1988;64:772-4.
14. Adler M, Quenon M, Even-Adin D, et al. Whole gut lavage for colonoscopy: A comparison between two solutions. Gastrointest Endosc. 1984;30:65-7.
15. Beck DE, Fazio VW, Jagleman DG. Comparison of oral lavage methods for preoperative colon cleansing. Dis Colon Rectum. 1986;29:699-703.
16. Marshall JB, Pineda JJ, Barthel JS, et al. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol electrolyte lavage for colonoscopy preparation. Gastrointest Endosc. 1993;39:631-4.
17. Kim KS. Effect of clebopride, antidopaminergic gastrointestinal prokinetics, on cardiac repolarization. Int J Toxicol. 2007; 26(1):25-31.
18. Rhodes JB, Engstrom J, Stone KE. Metoclopramide reduces the distress associated with colon cleansing by an oral electrolyte overload. Gastrointest Endosc. 1978;24:162-3.
19. Froehlich F, Fried M, Schnegg JF, et al. Low sodium solution for colonic cleansing: A double blind, controlled, randomized prospective study. Gastrointest Endosc. 1992;38:579-81.
20. Huppertz-Hauss G, Bretthauer M, Sauar J, et al. Polyethylene glycol vs sodium phosphate in bowel cleansing for colonoscopy: A randomized trial. Endoscopy. 2005;37:537-41.