Japanese Journal of Gastroenterology and Hepatology

Clinical Paper

ISSN: 2435-1210 | Volume 9

Split-dose Lactulose with Adjunctive Oral Bisacodyl and Oral Sodium Phosphate: A Pilot Study of a Novel Bowel Preparation

Loh WL[1], Tan HYT[2*], Tan O[3], Tung J[3], Kabir T[1] and Ngoi SS[3]

[1]Singapore General Hospital, Outram Road, Singapore

[2]National University Hospital, 5 Lower Kent Ridge Road, Singapore

[3]Gleneagles Hospital, 6A Napier Road, Singapore

***Corresponding author:**

Hwee Yong Trevor Tan,
National University Hospital, 5 Lower Kent Ridge Road, 16 Siglap Plain, S456005, Singapore, Tel: +65 64430800; E-mail: trevortan_hy@outlook.sg

Received: 05 Sep 2022
Accepted: 15 Sep 2022
Published: 20 Sep 2022
J Short Name: JJGH

Citation:

Tan HYT. Split-dose Lactulose with Adjunctive Oral Bisacodyl and Oral Sodium Phosphate: A Pilot Study of a Novel Bowel Preparation. J Gstro Hepato. V9(8): 1-6

Keywords:

Split-dose; Bowel preparation; Lactulose

1. Abstract

1.1. Background: Various colonoscopic bowel preparations are in use clinically. Split-dose preparations are generally recommended for morning colonoscopies. We herein present a novel form of bowel preparation with split-dose lactulose as the backbone with oral bisacodyl and sodium phosphate, in a pilot study assessing its safety and efficacy.

1.2. Method: Patients were instructed to adhere to clear fluids from 2000hrs the evening before. The bowel preparation utilised oral lactulose 30 mLs and bisacodyl 5 mg at 2200hrs the evening before, followed by oral lactulose 100 mLs and oral aqueous sodium phosphate 20 mLs four hours prior to the scheduled colonoscopy. All colonoscopies were carried out during the morning session. Patients' demographics, past medical and surgical history, indication for colonoscopy, tolerability, presence of side effects, colonoscopy findings, and bowel preparation cleanliness were recorded.

1.3. Results: This pilot study consisted of 82 patients with 41 females (50%), with a median age of 57 years (range 22 to 78). The most common indication for colonoscopy was abdominal pain (43 patients, 52.4%). 78 patients (95.1%) completed their bowel preparation, with only two patients (2.4%) suffering from side effects (vomiting). Median time to reaching the cecum was five minutes (median 3-25), and withdrawal time was 14 minutes (median 10-39). 55 patients (67.1%) and six patients (7.3%) had polyps and a malignancy detected respectively. 0 patients (0%), five patients (6.1%), 45 patients (54.9%), 32 patients (39.0%) had inadequate, poor, good, and excellent bowel preparation as per the Boston Bowel Preparation Scale.

1.4. Conclusions: This novel split-dose bowel preparation is safe, well-tolerated, and efficacious in selected patients. It should be assessed against other established preparations in future studies.

'What does this paper add to the literature?'

This paper describes a novel split-dose preparation, which might potentially be useful in selected patient populations.

2. Background

Colonoscopy has become an important tool for colorectal cancer screening in addition to investigating symptoms possibly related to the lower gastrointestinal tract, being the only modality that offers both diagnostic and therapeutic capabilities [1]. The rate of inadequate bowel preparation can be as high as 25% based on large multi-centred and national studies [2, 3]. Performing colonoscopy with suboptimal bowel preparation can increase the risk of adverse events, lengthen insertion and overall procedure times, require reducing the interval between procedures, lower cecal intubation and adenoma detection rates [4, 5].

In 2006, the American Society of Colon and Rectal Cancer (ASCRS), American Society of Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) issued a joint statement that stated that a colonoscopy preparation should have the following properties: inexpensive; cleanse the bowels rapidly; and not cause significant patient discomfort or electrolyte imbalances [6]. In addition, a good bowel prepara-

tion should be safe, tolerable, and efficacious.

Lactulose is a disaccharide, semi-synthetic derivative of lactose. After absorption, bacterial action causes fermentation, which acidifies the environment and causes acceleration of intestinal transit by stimulating motility and increased osmotic pressure [7]. Bisacodyl irritates the smooth muscles of intestines and the colonic intramural plexus hence increasing peristalsis. In addition, it increases accumulation of intestinal fluid by altering water and electrolyte secretion [8]. Sodium phosphate has on osmotic effect, increasing intraluminal fluid and promoting peristalsis [9].

In this pilot study, we sought to evaluate a novel split-dose bowel preparation with oral lactulose as the backbone with adjunctive oral bisacodyl and oral aqueous sodium phosphate in a carefully selected patient population based upon safety, tolerability and efficacy.

3. Methods

All patients recruited were scheduled for morning session colonoscopies. Patients were instructed to have a low-residue diet the day before and clear fluids from 2000hrs the evening before the colonoscopy. The bowel preparation utilised oral lactulose 30 mLs and bisacodyl 5mg at 2200hrs the evening before, followed by oral lactulose 100 mLs and oral aqueous sodium phosphate 20 mLs four hours prior to the scheduled colonoscopy. Each patient was given written and verbal instructions on the bowel preparation, and advised to hydrate themselves adequately though no volume of liquids was specified. All colonoscopies were performed under monitored sedation.

Patients' demographics, past medical and surgical history, indication for colonoscopy, tolerability, and presence of side effects, colonoscopy findings, and colonoscopy details including bowel cleanliness were recorded. Demographics, medical history and indication for colonoscopy were recorded upon recruitment. Tolerability and side effects were recorded prior to the start of colonoscopy while the patient was in the endoscopy suite reception. Colonoscopy details were recorded at the end of the procedure immediately.

The inclusion criteria were patients above the age of 18 who had any indication for colonoscopy and were physically fit for the procedure under sedation. The bowel preparation under study included oral lactulose, oral bisacodyl, and oral sodium phosphate, which is not recommended in certain patient populations due to concerns of side effects. Hence the exclusion criteria were: 1. Patients with heart failure (New York Heart Association class III or IV or ejection fraction <50 percent), 2. Renal insufficiency (creatinine clearance <60 mL/min/1.73m2), 3. End-stage liver disease, 4. Patients on diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, or other drugs that affect renal perfusion or function (due to increased risk of electrolyte abnormalities, dehydration, acute phosphate nephropathy).10 5. galactosemia (galactose-sensitive diet), 6. Long Q-T syndrome, 7. Patients with possible bowel obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon, ileus, 8. Patients with a history of inflammatory bowel disease. 9. Be pregnant or nursing, 10. Patients less than 18 years of age, or above the age of 80 years, 11. Inability to understand the requirements of the study or be unwilling to provide written informed consent and agree to abide by the study restrictions.

Patients were followed up at 15 days at the clinic and 30 days post-procedure by telephone to assess for any late complications.

A single operator (SSN) performed all the colonoscopies in the same endoscopy suite.

4. Results

A total of 82 patients were recruited for the pilot study, of which 41 (50%) were female. The median age was 57 years (range 22-78). The population recruited was relatively healthy due to the exclusion criteria applied, with 15 patients (18.3%) having hypertension, 12 patients (14.6%) having hyperlipidemia, four patients (4.9%) having diabetes mellitus, two patients (2.4%) having ischemic heart disease. No patients in the pilot study group had congestive cardiac failure, prior cerebrovascular accident, chronic renal failure, cirrhosis, or pulmonary disease. Only four patients (4.9%) had previous abdominal surgery, with two patients having had prior anterior resections, one patient with prior right hemicolectomy, and one patient with prior gastric resection. The majority of patients (67 patients, 81.7%) had one clinically relevant indication for colonoscopy. The most common indication for colonoscopy was abdominal pain or discomfort (43 patients, 52.4%). 36 patients (43.9%) had a previous colonoscopy before. These demographic details are summarised in Table 1 and 2.

78 patients (95.1%) completed the prescribed bowel preparation. Of the four patients that failed to complete the bowel preparation, one case was due to the side effect of vomiting, whilst three cases were due to miscommunication. The bowel preparation in question was very well tolerated, with only two patients (2.4%) suffering from the side effect of vomiting. On whether they would be willing to undergo the same bowel preparation, the majority of patients (61 patients, 74.4%), whilst 19 patients (23.2%) replied in the affirmative, and two patients (2.4%) replied in the negative. The two patients who were not willing to undergo the same bowel preparation were the same two who suffered from the side effect of vomiting.

The median time interval between the completion of the bowel preparation and the start of colonoscopy was 154 minutes (range 105-607). The median time taken to reach the cecum was 5 minutes (range 3-25), and the median withdrawal time was 14 minutes (range 10-39). 55 patients (67.1%) had polyp(s) detected, and six patients (7.3%) had a malignancy detected. Based on the Boston Bowel Preparation Scale (BPSS), zero, five (6.1%), 45 (54.9%), and 32 (39.0%) patients had inadequate, poor, good and excellent bowel preparation respectively. There were no events of perforation, bleeding (primary or secondary), sepsis, post-polypectomy syndrome recorded.

Table 1: Patient's Demographics

Variable	Frequency (%) or Median (range)
Total Patients	82 (100.0)
Male	41 (50.0)
Female	41 (50.0)
Age	57 (22-78)
Past Medical History	
Hypertension	15 (18.3)
Hyperlipidemia	12 (14.6)
Diabetes Mellitus	4 (4.9)
Ischemic Heart Disease	2 (2.4)
Congestive Cardiac Failure	0 (0.0)
Cerebrovascular Accident	0 (0.0)
Chronic Renal Failure	0 (0.0)
Cirrhosis	0 (0.0)
Pulmonary Disease	0 (0.0)
Past Surgical History	4 (4.9)
Anterior Resection	2 (2.4)
Right Hemicolectomy	1 (1.2)
Gastric Resection	1 (1.2)
Indication for Colonoscopy	
1 indication	67 (81.7)
2 indications	15 (18.3)
Abdominal Pain/Discomfort	43 (52.4)
Change in Bowel Habit	18 (22.0)
Hematochezia	15 (18.3)
Screening	8 (9.8)
Surveillance	6 (7.3)
Abdominal Bloatedness	4 (4.9)
Loss of Weight and/or Appetite	1 (1.2)
Anemia	1 (1.2)
Suspected Malignancy	2 (2.4)
Prior Colonoscopy	
Yes	36 (43.9)
No	46 (56.1)
Completion of Bowel Preparation	
Yes	78 (95.1)
No	4 (4.9)
Reason for Incomplete Bowel Preparation	
Vomiting	1 (1.2)
Miscommunication	3 (3.7)
Side Effects	
Vomiting	2 (2.4)
Nausea	0 (0.0)
Severe Abdominal Colic	0 (0.0)
Giddiness	0 (0.0)
Fainting	0 (0.0)
Chest Pain	0 (0.0)
Incontinence	0 (0.0)
Willingness to Undergo Same Preparation	
Yes	19 (23.2)
No	2 (2.4)
Undecided	61 (74.4)

Table 2: Tolerability and Safety of Bowel Preparation

Variable	Frequency (%) or Median (range)
Time Interval Between Completion of Bowel Preparation and Start of Colonoscopy (Minutes)	154 (105-607)
Time to Cecum (Minutes)	5 (3-25)
Withdrawal Time (Minutes)	14 (10-39)
Polyp(s) Detected	
Yes	55 (67.1)
No	27 (32.9)
Location of Polyp(s)	
Right Colon	30 (36.6)
Transverse Colon	14 (17.1)
Left Colon	32 (39.0)
Rectum	11 (13.4)
Malignancy Detected	
Yes	6 (7.3)
No	76 (92.7)
Location of Malignancy	
Right Colon	0 (0.0)
Transverse Colon	1 (1.2)
Left Colon	2 (2.4)
Rectum	3 (3.7)
Boston Bowel Preparation Scale	
0-2	0 (0.0)
3-5	5 (6.1)
6-7	45 (54.9)
8-9	32 (39.0)

5. Discussion

Bowel preparation agents are classifiable in a variety of ways, including volume administered (low-volume versus high-volume), osmolarity (isotonic versus hypoosmotic versus hyperosmotic), or main active ingredient. Ideally, the bowel preparation used should be safe, efficacious, well tolerated, and reasonably priced. Many preparations and regimes exist in modern practice, and none have been universally adopted.

The most commonly used bowel preparation is polyethylene glycol electrolyte lavage solution (PEG-ELS), due to it's excellent safety profile with the minimal electrolyte shifts. However, the tolerability of large volume (up to four litres) has been an issue for many patients, and this has led to the use of low-volume (two litres) of PEG-ELS with an adjunct [1]. In a search for lower volume bowel preparations, hyperosmotic agents such as sodium phosphate, magnesium citrate, sodium sulfate, and sodium picosulfate have been used with some success, although their safety profile or lack of evaluation limits their use in patients with significant co-morbidities such as renal failure (sodium phosphate, sodium sulphate, magnesium citrate), congestive cardiac failure (sodium sulphate, cirrhosis (sodium sulphate, and the elderly (sodium picosulfate) [1].

The timing of bowel preparation in relation to colonoscopy is crucial, and a shorter interval (three to four hours, less than eight hours) from completion of bowel preparation to colonoscopy is recommended [11]. This has led to split-dose bowel preparations, and multiple studies have confirmed its improved cleansing properties and patient tolerability [12].

We sought in this pilot study with split-dose lactulose as the backbone with adjunctive to test out a novel bowel preparation. The theory is that a relatively low dose of lactulose the evening before would begin the process of bowel cleansing by way of increased motility and intraluminal fluid. The onset of the evening dose of bisacodyl (six-eight hours) would coincide approximately with the morning dose of high dose lactulose with oral sodium phosphate (both of which would act as a cathartic), helping to increase peristalsis and lessen abdominal distension.

Lactulose has been utilised in bowel preparations before, though not as a split-dose preparation. One small randomised controlled trial of 200 patients found that 120 mLs of lactulose diluted to one litre and consumed within one hour had less tolerability but equal efficacy to PEG-ELS [13]. In another controlled study of 90 patients, the addition of lactulose to PEG-ELS had better efficacy but with no

increase in adverse events [14]. To our knowledge, our study is the first to evaluate the safety and tolerability of split-dose lactulose as the main bowel cleansing agent.

In Europe and the United States of America, bisacodyl is avoided in bowel preparations due to concerns of ischemic colitis [15]. However, it is not uncommonly used in Japan, and we decided to employ it for the same purpose, as our population is mainly Asian in ethnicity and may respond similarly [16]. In our group of patients, no cases of ischemic colitis were noted either intra-procedurally by endoscopic imaging nor post-procedure by clinical symptoms and signs.

Sodium phosphate's safety profile limits its widespread use. The most notable but rare side effect is acute phosphate nephropathy, which can occur in patients with normal renal function and can be irreversible [17]. For the same reason, it is generally avoided in patients with chronic renal failure, congestive heart disease, and the elderly. It can also mimic colitis in patients with inflammatory bowel disease and should also be avoided in this population [18]. The dose of oral aqueous sodium phosphate used for bowel preparation routinely is 30-45 mLs (of 48 g Na2HPO4 -18 g Na2HPO4/100 mLs) x 2 10-12 hours apart. The dose used in our study (oral aqueous sodium phosphate 20 mLs) is significantly less than what is used in routine bowel preparation, as it is meant to be utilised as an adjunct to the backbone of lactulose. Nevertheless, to avoid potentially serious side effects, we explicitly avoided these susceptible populations in our pilot study. In our carefully selected population, there were no cases of nephropathy, colitis, overt dehydration or electrolyte disturbances.

Tolerability and safety profile in our patient population was excellent, with 95.1% of patients completing the prescribed bowel preparation, and 2.4% having side effects of vomiting and were not willing to undergo the same bowel preparation. Despite written and verbal instructions, three out of 82 patients did not complete the bowel preparation due to miscommunication. Educational videos have been shown to be useful in increasing patient compliance rate, bowel cleanliness, cecal intubation, and adenoma detection rate [19]. In future follow-up studies, an instructional video with clear instructions can be considered for recruited patients. This might be particularly relevant for our bowel preparation, which includes three different agents in split dosing, which can understandably be confusing for some patients.

We chose to use the BBPS for the grading of our bowel preparation as it validated and has excellent excellent intra- and interobserver reliability [20]. The overall score is calculated for a total of 0 to 9, with 0-2, 3-5, 6-7, 8-9 representing inadequate, poor, good and excellent preparation scores respectively. 93.9% of our patients had good to excellent bowel preparation. This is as efficacious as other published data [21]. However, this pilot study is not meant for a head-to-head comparison with other established bowel preparation regimens. In our population, no pre-procedural, intra-procedural nor post-procedural complications were recorded, supporting its safety profile preliminarily.

In summary, this pilot study suggests that our novel bowel preparation using a lactulose backbone with adjuncts is safe and efficacious in carefully selected populations. Future studies will be conducted to compare it to established regimens used widely in clinical practice.

References

1. Bechtold ML, Choudhary A. Bowel preparation prior to colonoscopy: a continual search for excellence. World J Gastroenterol. 2013; 19: 155-157.
2. Froehlich F, Wietlisbach V, Gonvers JJ, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: The European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc. 2005; 61: 378.
3. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc. 2003; 58: 76.
4. Rex DK, Imperiale TF, Latinovich DR, et al. Impact of bowel preparation on efficiency and cost of colonoscopy. Am J Gastroenterol. 2002; 97: 1696.
5. Chokshi RV, Hovis CE, Hollander T, et al. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. Gastrointest Endosc. 2012; 75: 1197.
6. Wexner SD, Beck DE, Baron TH, et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Dis Colon Rectum. 2006; 49: 792-809.
7. Schumann C. Medical, nutritional and technological properties of lactulose. An update. Eur J Nutr. 2002; 41: 17-25.
8. Manabe N, Cremonini F, Cameliier M, et al. Effects of bisacodyl on ascending colon emptying and overall colonic transit in healthy volunteers. Aliment Pharmacol Ther. 2009; 30: 930-6.
9. Adamcewicz M, Bearelly D, Porat G, et al. Mechanism of Action and Toxicities of Purgatives Used for Colonoscopy Preparation. Expert Opin Drug Metab Toxicol. 2011; 7: 89-101.
10. Johnson DA, Barkun AN, Cohen LB et al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the U.S. multi-society task force on colorectal cancer. Gastrointest Endosc. 2014; 80: 543.
11. Bryant RV, Schoeman SN, Schoeman MN. Shorter preparation to procedure interval for colonoscopy improves quality of bowel cleansing. Intern Med J. 2013; 43: 162-168.
12. Kilgore TW, Abdinoor AA, Szary NM, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a metaanalysis of randomized controlled trials. Gastrointest Endosc. 2011; 73: 1240-1245.
13. Menacho AM, Reimann A, Hirata LM, et al. Double-blind prospective randomized study comparing polyethylene glycol to lactulose for bowel preparation in colonoscopy. Arq Bras Cir Dig. 2014; 27: 9-12.
14. Lu J, Cao Q, Wang X, et al. Application of Oral Lactulose in Combination With Polyethylene Glycol Electrolyte Powder for Colonoscopy Bowel Preparation in Patients With Constipation. Am J Ther. 2016; 23: e1020-4.
15. Baudet JS, Castro V, Redondo I. Recurrent ischemic colitis induced by

colonoscopy bowel lavage. Am J Gastroenterol. 2010; 105: 700.

16. Mishima Y, Amano Y, Okita K, et al. Efficacy of prokinetic agents in improving bowel preparation for colonoscopy. Digestion. 2008; 77: 166-172.
17. Choi NK, Lee J, Chang Y, et al. Acute renal failure following oral sodium phosphate bowel preparation: a nationwide case-crossover study. Endoscopy. 2014; 46: 465-470.
18. Brousse N, Abdelli N, Grimaud JC, et al. Endoscopic and histological findings of colonic pseudo-lesions induced by Fleet Phospho-Soda(R). Gastroenterol Clin Biol. 2002; 26: 105-106.
19. Bearelly D, Kottewar S, Almashhrawi A, et al. Instructional video improves the quality of bowel preparation for colonoscopy. Am J Gastroenterol. 2014; 109: S599.
20. Calderwood AH, Schroy PC 3rd, Lieberman DA, et al. Boston Bowel Preparation Scale scores provide a standardized definition of adequate for describing bowel cleanliness. Gastrointest Endosc. 2014; 80: 269-276.
21. Clark BT, Protiva P, Nagar A, et al. Quantification of adequate bowel preparation for screening or surveillance colonoscopy in men. Gastroenterology. 2016; 150: 396-405.