Volume of fluid consumption during preparation for colonoscopy is possibly the single most important determinant of bowel preparation adequacy

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Abstract

Background The effectiveness and safety of colonoscopy are directly dependent on the quality of bowel preparation. Multiple risk factors for inadequate bowel preparation (IBP) have been identified; however, IBP is still reported in 20-30% of cases in most studies. We aimed to identify modifiable predictors of the adequacy of bowel preparation using sodium picosulfate, and to recommend easily modifiable parameters to increase the success rate of colonoscopies.

Methods This was a single-center observational study of adult outpatients referred for an elective colonoscopy. Patients were interviewed prior to colonoscopy; volume of liquids consumed was calculated as number of 200-mL cups showed to the patient. Additional information, including medical history, diagnoses and regular medications, was procured from patients' medical records. Univariate and multivariate regression analyses were performed to identify factors significantly associated with IBP in a subgroup analysis of high-risk patients.

Results The rate of IBP in 1172 subjects was 19.4%. This rate decreased as fluid consumption increased, with a further drop associated with shorter intervals from end of preparation to colonoscopy. Drinking < 1.4 L significantly increased the risk of IBP (odds ratio [OR] 3.62, 95% confidence interval [CI] 2.65-4.95), while drinking ≥2 L was associated with adequate preparation (OR 0.09, 95%CI 0-0.42). These associations were stronger in high-risk individuals.

Conclusion Greater fluid intake and short interval to colonoscopy are easily modifiable parameters that can substantially reduce the rate of IBP, especially among high-risk individuals.

Keywords Inadequate bowel preparation, colonoscopy, bowel cleansing, sodium picosulfate

Ann Gastroenterol 2021; 34 (5): 705-712

Introduction

The efficacy and safety of colonoscopy is highly dependent on the adequacy of bowel preparation [1-3]. Inadequate bowel

preparation (IBP) is associated with lower detection rates of both benign and malignant lesions, longer procedure times and a more frequent need for a repeat procedure, with a resulting loss of work days, additional colonoscopic procedural risk to the patient and greater cost [3-6]. The rate of IBP varies among multiple studies, ranging from 5-67%. A recently published, large-scale meta-analysis showed a calculated IBP rate of 19.9% [7]; therefore, improvement in preparation adequacy rate is crucial.

Previous studies have identified multiple risk factors associated with IBP [8-12]: e.g. sex and older age are weak predictors of IBP. Diabetes and underlying neurologic conditions—mainly dementia, stroke and Parkinson's disease—were consistently shown to be strong predictors of IBP in large-scale studies [9,10]. Various medications are associated with a higher risk of IBP, with opioids and tricyclic antidepressants being the strongest and most consistent in large-scale studies [10,11,13]. Factors associated with the preparation protocol (especially the effectiveness of split dose preparation and adding bisacodyl or senna to the standard preparation) were assessed in other studies, and were found

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to be mostly associated with better rates of adequate bowel preparation [14-17]. It has also been suggested that a delay between the end of preparation and the colonoscopy confers a higher risk for IBP [18-20]. However, most of the factors suggested by these studies are currently not modifiable, with the exception of shortening the time interval to the procedure (not always possible due to time of day) and splitting the dose of the medication chosen for preparation. In the current study, we sought to prospectively collect multiple patient characteristics, including modifiable factors associated with bowel preparation that have not been previously reported but could potentially be used to reduce IBP and improve the quality of colonoscopy.

Patients and methods

Design

We performed a prospective, single-center, observational study of adult outpatients undergoing colonoscopy, regardless of indication. The study took place between September 2016 and April 2018, at the Department of Gastroenterology, Rambam, Haifa, Israel. All subjects provided written informed consent. Included were adult patients referred for outpatient colonoscopy who had provided personal and medical information, as well as details concerning the bowel preparation procedure. Excluded were inpatients and patients who had undergone previous bariatric, small bowel, or colorectal surgical procedures. Patients with a previous history of other abdominal procedures, such as appendectomy or cholecystectomy, were included. The study protocol was approved in April 2016 by the Rambam institutional review board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Data collection

All demographic information, medical diagnoses, medications and indications for the procedure were extracted from patients' electronic medical records and physicians' referral letters. All patients were interviewed by a single nurse practitioner (EH) regarding preparation-related information, using a standard questionnaire prior to colonoscopy. After the first 452 patients, the data were analyzed and a decision was made to extend the questionnaire to include all previous questions with the addition of the new variables listed.

Demographic and social information, medical and surgical history, as well as medications and lifestyle habits (e.g. tobacco use) were collected. Data regarding medical history were reviewed with the patients and recorded, including chronic constipation (<3 bowel movements per week), diarrhea (>3 watery bowel movements per day), diabetes, inflammatory bowel disease, thyroid function disorder, rheumatic disease, heart disease, and neurological disorders such as previous cerebrovascular accident or Parkinson's disease. Subjects were queried as to when they had performed preparation steps, such as initiation of laxative sachets, as well as the time intervals between sachets and between laxative-initiated

diarrheal episodes. Subjects were also interviewed regarding compliance with the bowel preparation protocol, including diet, bisacodyl use and the volume of liquids consumed defined by number of 200-mL volume cups presented during the interview. Patients who completed the interview were included in the final analysis, irrespective of factors such as measures of compliance.

Bowel preparation

The recommended bowel preparation protocol, including written instructions, was mailed to all patients scheduled for an outpatient colonoscopy at Rambam. The preparation protocol consisted of split-dose Picolax® (sodium picosulfate together with magnesium citrate). Each dose consisted of 16.1 g sodium picosulfate with magnesium citrate, which patients were instructed to dissolve in a cup of water. Patients scheduled for a morning procedure were instructed to stop all solid food at 12:00 the day before the procedure and drink only clear liquids until 3 h before the procedure; they were instructed to drink the first sachet at 14:00 and the second sachet at 20:00 the day before the procedure. Patients scheduled for an afternoon examination were instructed to discontinue solid food at 18:00 and consume the first sachet at 20:00 the day before the procedure, and the second sachet at 08:00 the day of the procedure. Patients were recommended to drink 1.6 L (8 cups) of clear liquids following each sachet.

All patients were recommended to take 2 tablets of bisacodyl 5 mg q.d., starting 3 days prior to colonoscopy. A low-fiber diet was recommended for 3 days prior to the procedure. All medications, except for antidiabetics, were permitted, and antiplatelets and anticoagulants were discontinued according to standard guidelines [21]. Standard dose aspirin (75-325 mg) could be continued. During their interview, patients were shown a 200-mL cup and asked to estimate how many such cups of water, or any other clear liquid, they had consumed after each sachet. The main endpoint was bowel preparation adequacy as assessed during colonoscopy.

Endoscopists with various levels of expertise, ranging from fellows to highly experienced senior endoscopists, performed the colonoscopies and evaluated bowel preparations. Colonoscopies were performed using Olympus 160 and 185 series and Fuji 600 series endoscopy systems.

The adequacy of bowel preparation was graded by the endoscopist according to the Boston Bowel Preparation Scale (BBPS), as previously described [22]. In summary, the BBPS is based on a 4-point scoring system applied separately to each of the 3 main segments of the colon [22]. The summation of the 3 "segment scores" gives a total BBPS score ranging from 0-9. As previously recommended [21], bowel preparation was considered "good" if the BBPS was ≥6, and ≥2 in each colonic segment, or "inadequate" otherwise. A written explanation of the Boston scale was provided to the endoscopist upon request via the electronic endoscopic report.

Statistical analysis

The statistical analysis was performed using R version 3.4.0 (The R Foundation for Statistical Computing, Vienna,

Austria). All clinical variables were compared between the adequately and inadequately prepared subjects. Continuous variables were presented as medians with interquartile ranges, and then compared using a Mann-Whitney *U* test or Student's *t*-test, as appropriate. Dichotomous and categorical variables were presented as numbers, percentages and odds ratios (OR), then compared using Fisher's exact test and univariate logistic regression analysis, respectively, with the most frequent factor used as reference for categorical variables. Some continuous variables, such as the time interval from the end of preparation to the initiation of colonoscopy and any fluid consumption, were also analyzed as dichotomous or categorical variables for representative constructs (e.g. <8 or >8 h from end of preparation to initiation of colonoscopy). Multivariate regression analysis was performed for variables that showed a significant difference between the adequate and inadequate preparation groups. To account for variability in preparation adequacy between endoscopists, an additional multivariate analysis was performed with the previously found predictors along with the performing endoscopist.

Results

Of the 1172 subjects who participated, 452 answered the original questionnaire and 720 the extended questionnaire; 619 (52.8%) were males, and the mean age was 55.8 years. Baseline demographic characteristics of the subjects are presented in Table 1. Twenty-four endoscopists performed the examinations, with a median number of 33 colonoscopies per endoscopist.

IBP was found in 227 (19.4%) subjects. A comparison of the demographic information, medical history and medications in the adequately and inadequately prepared subject groups, along with the ORs, is presented in Table 2. Typical colonoscopy images of adequately and inadequately prepared bowel segments seen during the study are presented in Fig. 1. In the univariate analysis, subjects with IBP were significantly older (mean age 60 vs. 58 years in the inadequately and adequately prepared groups, respectively; P=0.013) and weighed more than adequately prepared subjects (80 vs. 76 kg, respectively; P<0.001). Diabetes (35.2% of inadequately prepared vs. 19.4% of adequately prepared subjects, OR 2.26, 95% confidence interval [CI] 1.6-3.14; P<0.001), history of psychiatric disease (11% of the IBP vs. 5.6% of adequately prepared subjects, OR 2.08, 95%CI 1.21-3.5; P=0.007), and heart disease (22% of the IBP vs. 14.2% of adequately prepared subjects, OR 1.71, 95%CI 1.16-2.49; P=0.006) were shown to be significantly associated with IBP. In addition, the use of several medication groups was also significantly associated with a higher risk of IBP. These included proton pump inhibitors, anti-hypertensives, statins, and diuretics, among others (Table 2).

A similar comparison of adequately and inadequately prepared patients for variables subsequently added to the second questionnaire (n=720) is presented in Table 3. Education level significantly affected the risk of IBP; subjects with <12 years of education had a significantly higher risk for IBP (OR 3.06, 95%CI 1.88-4.33) than those with academic education (bachelor's or an associate degree). In addition to weight, included in

Table 1 Baseline characteristics of the entire patient cohort (n=1172)

Variable	Value (%)
Female, n (%)	533 (47.2)
Age, median (IQR), years	58 (20)
Weight, median (IQR), kg	77 (23.2)
Comorbidities, n (%)	
Previous abdominal surgery	480 (40.9)
Heart failure	184 (15.6)
Diabetes	223 (22.4)
Psychiatric disease	78 (6.6)
IBD	144 (12.3)
Medications, n (%)	
PPI	166 (14.2)
Antihypertensives	500 (42.7)
Statins	457 (39)
Antidepressants	49 (4.2)
Antipsychotics	85 (7.2)
Diuretics	58 (4.9)
Iron supplements	75 (6.4)
Opioids	13 (1.1)

IQR, interquartile range; IBD, inflammatory bowel disease; PPI, proton pump inhibitors

the original cohort, body mass index (BMI) was added to the extended questionnaires; as with weight, obesity (BMI ≥30 kg/m²) conferred a higher risk for IBP (OR 1.84, 95%CI 1.2-2.78). A subgroup analysis of various antidiabetic medications in diabetic patients did not reveal significant differences in the risk of IBP for any of the medications, including insulin. The use of 5 or more medication groups, not limited to those specifically mentioned above, was considered as polypharmacy and was associated with a significantly higher risk of IBP (OR 2.49, 95%CI 1.65-3.75). These associations were not found in the multivariate analysis.

Multiple parameters of the bowel preparation process were analyzed. A comparison of these variables between adequately and inadequately prepared patients is shown in Table 4. Adequate cleaning of the right colon (BBPS ≥2) was recorded in all adequately prepared patients and in only 42/227 (18.5%) of the inadequately prepared patients.

An interval of more than 8 h from the end of preparation to the beginning of the examination conferred a significantly higher risk for IBP, irrespectively of the time of the procedure (54.6% of the inadequately prepared vs. 41.3% of adequately prepared subjects, OR 1.71, 95%CI 1.27-2.32; P<0.001). In addition, higher rates of IBP were seen as the time from end of preparation to colonoscopy increased (Fig. 2A). An analysis comparing the volume of fluids consumed during preparation and adequacy showed that compared to subjects who drank 1.4L-2.0L of clear liquids subjects who drank <1.4 L after each sachet had a significantly higher risk of IBP (OR 3.62, 95%CI 2.65-4.95). Subjects who drank >2 L of liquids were substantially more likely to have a successful preparation (OR 0.09, 95%CI 0-0.42).

Table 2 Patient demographic and clinical variables. Univariate comparison between adequate and inadequate preparation

Variable	Adequately prepared (n=945, 80.6%)	Inadequately prepared (n=227, 19.4%)	P-value	OR for inadequate preparation (95%CI)
Age (years)	58 (21)	60 (18)	0.01*	
Female, n (%)	459 (48.6%)	94 (41.4%)	0.05	0.75 (0.55-1.01)
Weight (kg)	76 (22)	80 (22)	<0.01	
Comorbidities, n (%)				
Abdominal surgery (not including bowel procedures)	387 (41)	93 (41)	>0.99	1 (0.74-1.36)
Diabetes	183 (19.4)	80 (35.2)	<0.01	2.26 (1.63-3.14)
Heart disease	134 (14.2)	50 (22)	0.01	1.71 (1.16-2.49)*
Chronic kidney disease	34 (3.6)	13 (5.7)	0.19	1.63 (0.77-3.23)
Neurologic disorder	55 (5.8)	19 (8.4)	0.17	1.48 (0.81-2.59)
Rheumatic disease	56 (5.9)	13 (5.7)	>0.99	0.96 (0.47-1.83)
IBD	119 (12.6)	25 (11)	0.57	0.86 (0.52-1.37)
Psychiatric disease	53 (5.6)	25 (11)	0.01	2.08 (1.21-3.5)
Hypothyroidism	103 (10.9)	23 (10.1)	0.81	0.92 (0.55-1.5)
Medications, n (%)				
Proton pump inhibitors	117 (12.4)	49 (21.6)	<0.01	1.95 (1.31-2.86)
Antidepressants	40 (4.2)	19 (8.4)	0.02	2.07 (1.11-3.74)*
Antipsychotics	61 (6.5)	24 (10.6)	0.05	1.71 (1.00-2.87)*
Diuretics	37 (3.9)	21 (9.3)	<0.01	2.5 (1.36-4.49)*
Iron supplementation	55 (5.8)	20 (8.8)	0.13	1.56 (0.87-2.72)
Opioids	7 (0.7)	6 (2.6)	0.03	3.63 (1.00-12.76)*
Antihypertensives	377 (39.9)	123 (54.2)	<0.01	1.78 (1.32-2.41)*
Statins	342 (36.2)	115 (50.7)	<0.01	1.81 (1.34-2.45)*
Thyroid hormone replacement	79 (8.4)	22 (9.7)	0.15	1.18 (0.68-1.96)

*Non-significant when adjusted in multivariate analysis for weight, diabetes and fluid consumption

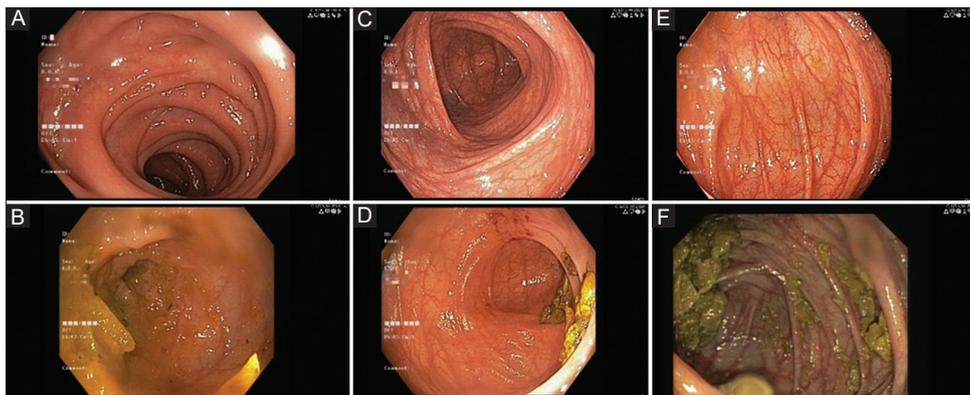*OR, odds ratio; CI, confidence interval; IBD, inflammatory bowel disease*

Figure 1 Typical colonoscopy images of adequately and inadequately prepared bowel segments seen during the study. Images taken in the Rambam healthcare campus endoscopy suite. Images include adequately and inadequately prepared left colon (A and B respectively); adequately and inadequately prepared transverse colon (C and D respectively); and, adequately and inadequately prepared left colon (E and F respectively)

Moreover, out of 66 subjects who drank >2 L of fluids after each sachet, only one had inadequate preparation. A logistic regression of the rate of IBP plotted against volume of liquids consumed within a short time interval to colonoscopy, compared to all other patients, is shown in Fig. 2B. The IBP rate dropped consistently as the volume of liquids consumed increased, with a further drop of up to an approximate 50% for subjects who also had a short interval between end of preparation and colonoscopy.

Table 3 Summary and comparison between patients with adequate and inadequate preparation. Demographic and clinical variables collected in the second (extended) questionnaire only

Variable	Adequately prepared (n=579, 80.4%)	Inadequately prepared (n=141, 19.6%)	P-value	OR for inadequate preparation (95%CI)
Height, median (IQR), cm	168 (13)	170 (13)	0.03*	
BMI, median (IQR), kg/m²	26.3 (5.9)	27.5 (6.7)	<0.01	
Obese (BMI ≥30 kg/m²): n (%)	127 (21.9)	48 (34)	<0.01	1.84 (1.2-2.78)*
Smoking: n (%)	92 (15.9)	30 (21.3)	0.13	1.43 (0.87-2.31)
Pack-years	15 (20.7)	15 (21.8)	0.6	0.79 (0.53-1.17)
Regular exercise: n (%)	216 (37.3)	43 (30.5)	0.14	0.74 (0.48-1.11)
Carbonated drinks (≥2 per week): n (%)	154 (26.6)	51 (36.2)	0.03	1.56 (1.03-2.35)*
Marital status				
Married	450 (77.7)	107 (75.9)		Reference
Single	86 (14.9)	13 (9.2)		0.64 (0.33-1.14)
Widower	24 (4.1)	11 (7.8)		1.93 (0.88-3.97)
Divorcee	19 (3.3)	10 (7.1)		2.21 (0.96-4.8)
Education level, n (%)				
Bachelor's or associate degree	392 (67.7)	65 (46)		Reference
Less than 12 years	71 (12.2)	36 (25.5)		3.06 (1.88-4.33)
12 years	116 (20)	40 (28)		2.08 (1.33-3.24)
Bowel habits, n (%)				
Normal	749 (79.3)	173 (76.2)		Reference
Diarrhea	81 (8.5)	17 (7.5)		0.91 (0.51-1.53)
Constipation	115 (12.2)	37 (16.3)		1.39 (0.92-2.07)
Nationality, n (%)				
Ashkenazi Jew	333 (57.5)	60 (42.5)		Reference*
Sephardic Jew	142 (24.5)	38 (26.9)		1.48 (0.94-2.32)
Arab Muslim	48 (8.3)	21 (14.9)		2.43 (1.34-4.3)
Arab Christian	38 (6.6)	12 (8.5)		1.75 (0.84-3.46)
Druze	18 (3.1)	10 (7.1)		3.1 (1.31-6.9)
Comorbidities: n (%)				
Pulmonary disease	30 (5.2)	19 (13.5)	<0.01	2.84 (1.46-5.42)
HbA1C†, median (IQR), %	6.8 (1.4)	6.8 (1.2)	0.77	
Medications, n (%)				
Polypharmacy (≥5 different medication groups)	121 (20.9)	56 (39.7)	<0.01	2.49 (1.65-3.75)*
Insulin†	34 (5.9)	19 (13.5)	0.47	1.31 (0.61-2.76)
Sulfonylurea†	16 (13.6)	2 (3.8)	0.06	0.26 (0.03-1.16)
Metformin†	88 (74.6)	42 (80.8)	0.44	1.43 (0.61-3.59)
DPP4 inhibitors†	26 (22)	9 (17.3)	0.54	0.74 (0.28-1.81)

* Non-significant when adjusted in multivariate analysis for weight, education level, diabetes, and fluid consumption

† Subgroup analysis of diabetic patients

OR, odds ratio; CI, confidence interval; IQR, interquartile range; BMI, body mass index; HbA1C, glycosylated hemoglobin; DPP4, dipeptidyl peptidase-4

Multivariate regression analysis that included multiple factors significantly associated with IBP on univariate analysis, along with the performing endoscopist, showed that only weight, presence of diabetes, psychiatric disease, volume of fluids consumed, and time interval to colonoscopy were significantly associated with an elevated risk for IBP in the entire cohort (n=1172). ORs and 95%CIs of the multivariate regression analysis results are shown in Table 5.

Table 4 Summary and comparison of bowel preparation related variable between patients with adequate and inadequate bowel preparation

Variable	Adequately prepared (n=945, 80.6%)	Inadequately prepared (n=227, 19.4%)	P-value	OR for inadequate preparation (95%CI)
Time between Picolax sachets (h)	6 (6)	6 (6)	0.22	
Time between 1st sachet and bowel movement (h)	2 (2)	2 (2)	0.11	
Time between 2nd sachet and bowel movement (h)	1 (0.5)	1 (1.5)	0.13	
Time between end of preparation to colonoscopy (h)	6 (7)	9 (7.5)	<0.01	
More than 8 h, n (%)	390 (41.3)	124 (54.6)	<0.01	1.71 (1.27-2.32)
Afternoon exam, n (%)	352 (37.2)	56 (24.7)	<0.01	0.55 (0.39-0.77)
Bisacodyl use, n (%)	811 (85.8)	203 (89.4)	0.16	1.40 (0.87-2.32)
Total bisacodyl (tablets)	4 (3)	4 (3)		0.79
Volume of liquids after each sachet,	1600 (400)	1500 (500)	<0.01	
<1.4 L, n (%)	172 (18.2)	105 (46.6)	<0.01	3.62 (2.65-4.95)
1.4L-2.0 L, n (%)	706 (74.9)	119 (52.9)	0.02	Reference
>2.0 L, n (%)	65 (6.9)	1 (0.4)		0.09 (0-0.42)
Bowel movements	8 (4)	6 (3)		<0.001
BBPS, median (IQR)	8 (2)	5 (2)		<0.001

OR, odds ratio; CI, confidence interval; BBPS, Boston bowel preparation score; IQR, interquartile range
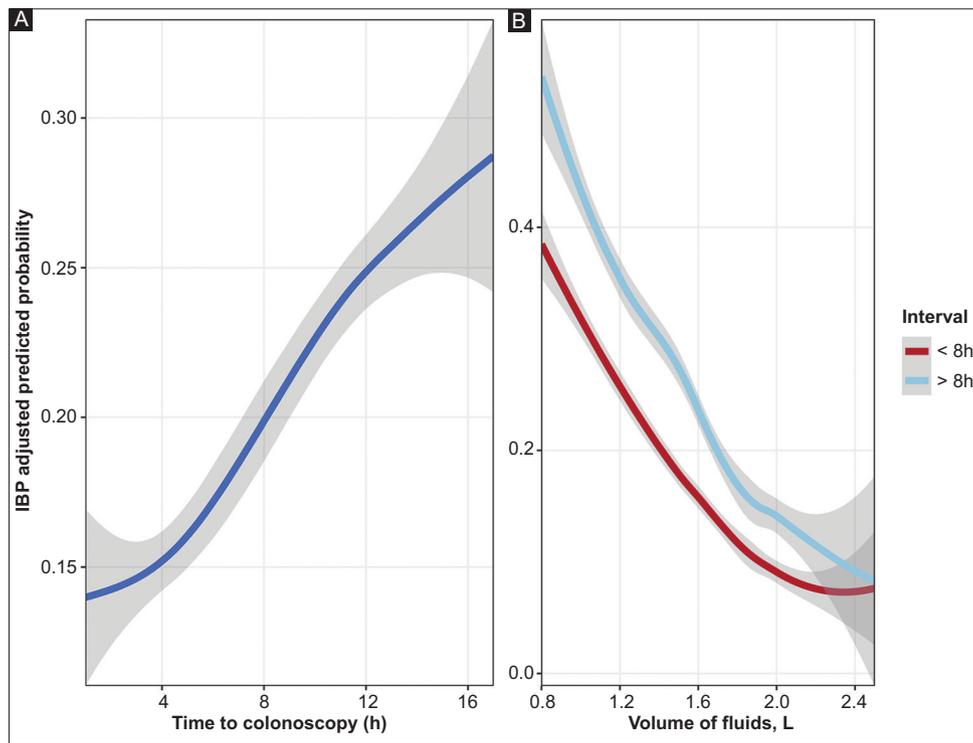

Figure 2 Predicted probability of inadequate bowel preparation (IBP) adjusted for variables significantly associated with IBP. A function of time (h) from end of preparation to colonoscopy (A) and volume of clear liquids consumed after each sachet of picosulfate, stratified by time to colonoscopy (B). Grey outlines represent the standard errors of the models

We further analyzed a subgroup of patients with favorable preparation features (drank ≥1.6 L of liquids and waited ≤8 h between end of preparation and beginning of examination). In this group, only 41/487 (8.4%) failed bowel preparation, compared to an IBP rate of 27% in the 685 patients who either drank <1.6 L of fluid or had their examination delayed (P<0.001). A subgroup analysis of patients at high risk for IBP, such as diabetics or individuals weighing more than 90 kg, revealed that among 96 diabetic individuals with both favorable features, inadequate preparation was seen in only 11 (11.5%), while 69/167

Table 5 Multivariate analysis of factors significantly associated with inadequate bowel preparation

Variable	Adjusted OR (95%CI)
Diabetes	1.95 (1.37-2.76)
Weight (odds ratio per 1 kg increase)	1.01 (1.005-1.02)
Psychiatric disease	1.96 (1.13-3.31)
Volume of liquids (odds ratio per 200 mL increase)	0.73 (0.68-0.8)
Examination delay (>8 h)	1.48 (1.09-2.02)

OR, odds ratio; CI, confidence interval

(36.9%) of diabetic patients who did not have both features failed preparation (P<0.001). Only 10/114 (8.8%) subjects with both favorable features who weighed 90 kg or more failed preparation, in comparison to a failed preparation in 61/167 (36.5%) subjects with this weight but without both favorable parameters (P<0.001).

Discussion

Adequate bowel preparation is essential for ideal endoscopic diagnostic yield. In this study, we prospectively studied 1172 patients in order to: 1) identify features associated with a high risk for IBP; 2) compare these findings to previous reports; and 3) search for bowel preparation features that can easily be modified and implemented into bowel preparation protocols to potentially lower the rate of IBP, particularly in high-risk individuals.

The rate of IBP in our cohort was 19.4%, similar to the IBP rates found in other studies, including a recent large meta-analysis performed by Mahmood *et al* [7,21]. The adequacy of bowel preparation, graded according to the BBPS, was also similar to other studies where preparation was mostly with sodium picosulfate [23,24]. Multivariate adjustment revealed unmodifiable variables (e.g. obesity, diabetes, and education level) significantly associated with IBP, all of which are well-established risk factors in the literature [7,8]. Interestingly, and consistently with previous findings, a higher BMI tended to raise the risk of IBP significantly, especially in males [8], though our study had a male predominance. Moreover, when females alone were analyzed, the effects of weight and BMI were attenuated (OR for obesity as a risk factor for IBP in females alone was 1.75, 95%CI 0.93-3.24). When multiple medication groups were assessed (e.g. opiates, anti-hypertensive drugs, and lipid lowering drugs) some were shown to be associated with IBP, similarly to previous reports [7,8]. Additionally, polypharmacy was associated with an increased risk of IBP, regardless of medication type (Table 3). While this association has been demonstrated previously [19], in our study this finding was not significantly associated with IBP after adjustment for multiple other factors (Tables 3,5).

Extensive bowel preparation characteristics were collected and analyzed, including volume of clear liquids consumed during colonoscopy preparation, which to the best of our knowledge has not been previously reported. We show that the volume of liquids consumed with each sachet was independently associated with the rate of IBP, where

only 1/66 patients who consumed ≥2 L after each sachet had inadequate preparation. Furthermore, this is the first study to show a direct and continuous association between volume of fluids consumed and IBP rate. This continuous reduction in rate was seen as fluid consumption exceeded the instructions provided in the picosulfate leaflet, which recommends at least 1.25 L (5 cups) and only 750 mL (3 cups or 250 mL) of clear liquids following the first and second sachets, respectively. In an effort to identify additional modifiable preparation-related features, we observed that the rate of IBP decreased further in a subgroup of patients whose colonoscopies were performed <8 h after they took the second sachet of sodium picosulfate. This finding was independent of whether the procedure took place during morning or afternoon hours. IBP rates were low even in high-risk diabetic, obese, or older patients who met this criterion. A longer time interval between bowel preparation and colonoscopy has long been shown to be a risk factor for IBP [7,8]; however, the further improvement we found with greater liquid consumption has major significance. An important reservation regarding these findings is the possible risk of electrolyte disturbances with consumption of high volumes of water during bowel preparation. Our subjects were outpatients and we did not perform any blood sample analysis. Therefore, further research is needed, and balanced fluids should be considered when high-volume preparations are recommended or studied. However, we are unaware of any hospitalizations or deaths that occurred in our cohort.

Several limitations of our study need to be addressed. Data were collected through questionnaires filled out by the patient with the assistance of a nurse practitioner immediately prior to colonoscopy, and therefore patient recall might cause bias with regard to clinical as well as preparation-associated information. Moreover, it is likely that subjects would feel some degree of unease about admitting to poor compliance with the preparation protocol. The large number of patients assessed in this study may alleviate this potential bias. Furthermore, this study was conducted in a single tertiary center in Israel, which might affect the generalizability of the results. However, our cohort was demographically diverse and included a variety of ages, ethnicities and educational backgrounds, which may have mitigated the aforementioned drawback. Since all patients were scheduled for an elective examination, the indication for colonoscopy was not recorded, though this information could have helped identify subgroups that would benefit from high-volume fluid preparation. Another substantial limitation is the difficulty of achieving full adherence to guidelines and mainly the strong recommendation of initiation of colonoscopy within 5 h of consumption of the last dose of bowel preparation [21]. The difficulty, especially with early morning examinations, is a well-known challenge. The lack of post-procedure follow up for any adverse effects is an additional limitation. However, we are unaware of any preparation-associated post colonoscopy hospitalizations. Finally, since all subjects in the study used sodium picosulfate for preparation, results might not be generalizable to other preparation protocols and further investigations are required.

In conclusion, along with previously suggested risk factors for IBP, also found in the current study, herein we show 2

modifiable bowel preparation factors, low fluid intake and a long interval to colonoscopy, that can easily be incorporated into preparation protocols to improve bowel preparation with sodium picosulfate. Further prospective interventional studies will be necessary before definitive conclusions can be drawn.

Summary Box

What is already known:

- Inadequate bowel preparation (IBP) is associated with reduced visualization, missed lesions, and an increased risk of colonoscopy
- A large meta-analysis estimated the median rate of IBP to be 26%
- Multiple risk factors for IBP have been identified, including age, comorbidities such as obesity and diabetes, use of specific medications, and a long interval between end of bowel preparation and colonoscopy
- Other than compliance with preparation protocols, there are few easily modifiable risk factors for IBP

What the new findings are:

- The volume of liquids consumed with each sachet was highly associated with the rates of IBP
- Increasing rates of IBP were observed in a continuous relation with longer time intervals between end of preparation and colonoscopy
- The combination of a larger volume of fluids consumed during the preparation, as well as a <8-h gap between the end of preparation and colonoscopy, additively reduced the rate of IBP
- Even in diabetic individuals at risk for preparation failure, low rates of IBP were observed in the group that consumed a large volume of fluids and had a short interval to colonoscopy

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