International Journal of
Health Systems and Medical Sciences

ISSN: 2833-7433
Volume 2 | No 12 | Dec -2023

Proper Bowel Preparation for Fibrocolonoscopy from the Point of View of Evidence-Based Medicine

Kadirov Bekhruzbek Saidovich [1]

[1] Bukhara state medical institute

Abstract: The article, from the perspective of evidence-based medicine, examines the role of adequate bowel preparation in increasing the effectiveness of fibrocolonoscopy, formulates modern requirements for drugs to prepare for this procedure, and demonstrates the advantages of second-generation sulfate-free drugs based on macrogol. The main ways to improve compliance and increase the efficiency of bowel preparation, including the use of two-stage regimens, are considered; a reduction in the volume of solution for intestinal lavage and the use of combined regimens are justified.

Keywords: bisacodyl, macrogol, bowel preparation, fibrocolonoscopy, endofalk.

Introduction. The success and tolerability of fibro colonoscopy (FCS), as well as the effectiveness of X-ray examination or surgical intervention on the abdominal organs, largely depend on effective bowel preparation. The proportion of cases of poor bowel preparation for examination is very high and, according to various sources, ranges from 20 to 40% [24]. According to P.L. Shcherbakova et al. [2], inadequate bowel preparation can cause late diagnosis of many serious diseases, including colorectal cancer, and also lead to significant additional costs for re-preparing the patient and for repeat colonoscopy. The most significant effect of inadequate bowel preparation is on the detection of small lesions of the colon - polyps and other neoplasms < 9 mm in size, reducing the likelihood of early diagnosis of both precancerous conditions and colon cancer [13]. A recently published systematic review and meta-analysis of 11 studies demonstrated a significantly higher incidence of colon adenomas with good bowel preparation (excellent, good or fair) compared with poor bowel preparation (OR - 1. 39-1.4) [30, 31]. In patients with inflammatory bowel disease (IBD), careful bowel preparation greatly facilitates the detection of IBD-associated neoplasia [21].

Achieving the proper quality of bowel preparation for colonoscopy is one of the most important clinical tasks, the solution of which can not only significantly increase the detection of organic intestinal pathology, but also reduce the costs of endoscopic examinations. Poor quality of bowel preparation reduces the economic efficiency of endoscopic procedures: inadequate bowel preparation significantly increases the duration of colonoscopy and in some cases requires a repeat examination, and with a more aggressive preparation regimen, according to current colorectal cancer screening programs.

To date, many methods have been proposed to optimize bowel movement, including various diets, laxatives, enemas and various intestinal lavage solutions. The main disadvantages of the traditional approach to bowel preparation using enemas, according to B.K. Poddubny et al. [1], are poor cleaning of the surface of the mucous membrane from intestinal contents; distortion of the endoscopic picture due to irritation of the mucous membrane with water and the enema tip; inability to satisfactorily prepare the right half of the colon and especially the ascending colon, the region of

the ileocecal valve and the terminal ileum; increased risk of colon perforation in common forms of diverticulosis; the use of additional equipment and the involvement of medical personnel for training. The use of stimulant or irritant laxatives (senna, bisacodyl, etc.) as monopreparations for bowel preparation is largely limited due to the need to use high doses of these drugs (for example, 264-288 mg for senna, 30-40 mg for bisacodyl), which significantly increases the frequency of side effects, such as abdominal discomfort and colicky/cramping pain, including significant intensity [1, 25, 28, 9]. The use of lactulose for bowel preparation is almost always accompanied by symptoms of flatulence, and therefore it is recommended to be prescribed only in conjunction with antifoam agents (simethicone). Many researchers note that the tolerability of lactulose is worse compared to macrogol. Side effects such as nausea and discomfort were more pronounced in patients taking lactulose, and the number of patients who were unable to complete bowel preparation with lactulose was 2.5 times higher than those using macrogol for this purpose [32]. Preparations based on sodium phosphate, which were widely used in the late 90s and were comparable in effectiveness to solutions based on macrogol, showed an unfavorable safety profile [11, 2]. They are not recommended for use in patients with renal failure, liver cirrhosis and chronic heart failure due to the risk of developing serious water and electrolyte disturbances such as hypernatremia, hypokalemia, hypocalcemia and hyperphosphatemia [23]. The US Food and Drug Administration (FDA) published 34 reports of adverse events associated with the use of sodium phosphate between 1997 and 2002, including 18 cases of serious adverse events. ¬nyami and 8 cases with fatal outcome [15]. These facts led the European Society of Gastrointestinal Endoscopy (ESGE) in 2013 to oppose the routine use of sodium phosphate for bowel preparation on safety grounds [14].

In terms of efficiency and safety, drugs containing macrogol (polyethylene glycol, PEG) occupy a leading position among all drugs used for bowel preparation, both for endoscopic examinations and surgical interventions [19]. The use of PEG in clinical practice (orthograde intestinal lavage), proposed back in 1980 by a group of researchers led by J.S. Fordtran [10] has revolutionized the practice of bowel preparation, both in outpatient and hospital settings. Meta-analyses and systematic reviews have demonstrated that PEG preparations have a significantly better safety profile than sodium phosphate-based preparations (with comparable effectiveness) and are also superior to all other bowel preparation methods that do not use sodium phosphate (OR = 2 .02, 95% CI1.08-3.78) [6, 7, 8, 22, 19]. PEG-based preparation regimens (as opposed to regimens using any other drug) provide significantly better quality of preparation of the proximal colon (OR = 2.36, 95% CI 1.16-4.77). This fact is important for the diagnosis of difficult-to-detect intestinal neoplasms with a predominant localization in the ascending colon - the so-called “flat” and “depressed” lesions (non-polyposis colorectal neoplasms) [18]. All current bowel preparation guidelines, including the latest ESGE guidelines, consider macrogol (PEG) as the drug of choice for routine bowel preparation for colonoscopy [14].

PEG preparations are represented by first-generation drugs (for example, the drug Fortrans, produced by Bofur Ipsen Industry, France). and second generation (for example, the drug Endofalk, Dr. Falk Pharma GmbH, Germany). All macrogol-containing drugs of the first generation contain sodium sulfate (as a factor in the osmolarity of the solution), which has an extremely unpleasant (nauseating, “vomiting”) taste. The poor taste of preparations containing sodium sulfate may reduce compliance and negatively affect patient compliance with instructions when preparing the intestines for colonoscopy, since to prepare for colonoscopy the patient needs to take about 4 liters of macrogol solution per liter. a relatively short period of time[27]. An increased concentration of PEG and a modified balance of electrolytes (compared to conventional solutions for intestinal lavage) made it possible to completely dispense with sodium sulfate in second-generation drugs, of which Endofalk is a representative.

The development of a sulfate-free macrogol-containing solution for intestinal lavage of the intestine, which underlies Endofalk, is based on the fundamental research of Fordtran J.S. et al. [12], who was able to demonstrate an almost neutral balance between the absorption and secretion of electrolytes and water. Clinically, a high degree of compliance has also been confirmed when using a sulfate-free PEG drug, primarily due to its pleasant taste [27]. The second generation of polyethylene glycol

preparations (macrogol 3350) does not contain sodium sulfate, but, due to the similar water-electrolyte balance and almost identical osmolarity (= 280 mOsm/kg), the clinical data obtained from the study of the first generation solutions may be without any or restrictions have been transferred to second-generation drugs.

However, despite the relatively good tolerance of PEG solutions, from 5 to 38% of patients cannot complete preparation for colonoscopy, mainly due to the large volume of solution (4 l) and the poor taste of preparations containing sodium sulfate [5, 4, 29].

There are several possible ways to improve compliance with bowel preparation for testing. The most effective of them involve the use of two-stage preparation regimens, the use of second-generation sulfate-free PEG preparations and the combination of a reduced volume PEG solution (2-3 l) with stimulant or osmotic laxatives [20]. An important indication for prescribing two-stage methods of colon preparation, which allows reducing the amount of liquid for preparation, is the suspicion that the patient has a stenotic tumor or non-tumor lesion of the colon (adhesive disease).

According to the results of numerous studies, a two-stage preparation scheme (split dosing, or split mode), dividing the dose into 2 days (the night before and in the morning on the day of colonoscopy), not only improves the tolerability of the preparation, but also significantly increases both the quality of preparation and the effectiveness of the research itself [17, 16].

One way to improve patient compliance by reducing the volume of solution taken is to combine 2 liters of PEG solution with a laxative. According to the American Consensus on the Preparation of Patients for Colonoscopy, the use of this regimen is a more acceptable alternative compared to the traditional administration of 4 liters of PEG solution, since “the regimen of 2 liters of PEG + bisacodyl solution ... is better tolerated by patients with the same quality of preparation using 4 liters of PEG solution” [29].

When using a regimen that includes PEG drugs and a laxative, there is less impact on the patient’s daily activity with a complete absence of negative reactions on his part [2]. We modified the scheme for the combined use of the second generation PEG drug (Endofalk) and bisacodyl, making it more universal and more personalized [33].

The study, which used a modified universal personalized scheme, providing for one- or two-stage bowel preparation depending on the nature of the patient’s stool on the morning of the FCS, was conducted at the Gastroenterology Clinic of the North-Western State Medical University. I.I. Mechnikova. This research program involved 30 patients aged 30 to 50 years with various pathologies of the digestive tract who required total FCS.

On the day before the study, the patient took bisacodyl at a dose of 10 mg or sodium picosulfate 7.5 mg (15 drops) (at about 14:00). Then, after the first act of defecation or 6 hours after taking bisacodyl/sodium picosulfate, the patient took 2 liters of second-generation PEG solution (in our case, 4 packets of the drug Endofalk were used - 1 packet per 0.5 liter of water) , distributing the drug in such a way that the last dose is taken no earlier than 20:30 and no later than 23:00. In the absence of stool in the morning on the day of the study, the presence of watery and clean (fecal-free and almost transparent) stool, or stool with a small amount of feces (type 6-7 on the Bristol scale), the patient no longer took Endofalk (one-step preparation). When an episode of fecal stool (type 4-5 on the Bristol scale) or any type of fecal stool with a large amount of feces appeared in the morning (but no later than 10:00), the patient additionally took 0.5-1 l of Endofalk (1-2 packages) (two-stage preparation).

Preparation scheme	Patients' assessment of the quality of preparation for FCS, points Me (Q1; Q3)	Doctors' assessment of the quality of preparation for the FCS, points Me (Q1; Q3)
Bisacodyl regimen	9,0 (8,0; 10,0)	8,5 (7,3; 9,0)
Scheme using sodium picosulfate	9,0 (9,0; 9,8)	8,0 (6,0; 8,5)

To assess the nature of the stool, its color and transparency, patients used the Bristol scale, as well as a new visual color scale developed at the Los Angeles Veterans Medical Center [26].

Patients were randomized to receive bisacodyl or sodium picosulfate using fixed block randomization with variable block size (randomly mixed permuted blocks). The endoscopist assessed the preparation for the study "blindly", without knowing which preparation scheme the patient used. To assess the quality of preparation (by both the patient and the endoscopist) on the day of the examination, the appropriate visual analog scales (VAS) were used.

Data processing included the following steps:

Analysis of the compliance of the quality of preparation for the FCS when assessed by the patient with the quality of preparation for the FCS when assessed by the doctor.

Comparison of the results of assessing the quality of preparation for FCS using regimens using bisacodyl/sodium picosulfate.

Assessment of the frequency of use of one-stage and two-stage preparation in the study group of patients.

Comparison of the results of assessing the quality of preparation for the FCS using one-stage and two-stage schemes.

Statistical data processing was carried out using the SPSS 17.0 software package (SPSS Inc., USA), using methods of descriptive statistics (median, quartiles), checking the distribution of variation series (Shapiro-Wilk test), correlation analysis (coefficient Spearman's rank correlation), comparison of independent observations (Mann-Whitney test), comparison of event frequencies (Fisher's exact test), calculation of confidence intervals (Wilson's method).

Since in this study the assessment of the quality of preparation for FCS was carried out by both patients and doctors, taking into account the different evaluative approaches of these two categories of study participants, at the initial stage of data processing it seems appropriate to study the possible relationship between the evaluative judgments of patients and doctors.

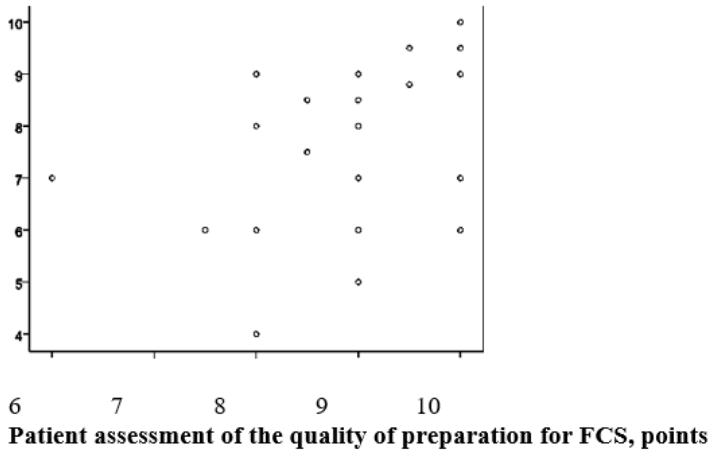

Fig. 1. Assessment of the relationship between the results of the scoring of the quality of preparation for FCS by the patient and the doctor.

A scatterogram constructed to search for a possible relationship between the results of the patient's and the doctor's scoring is presented in Fig. 1. The presented figure shows the heteroscedasticity of the distribution of observations, which is expressed in a chaotic scatter of points on the plane and allows us to reasonably exclude any linear relationship between two variation series, which is confirmed by the value and lack of statistical significance of the Spearman correlation coefficient (p = 0.332, p=0.073).

Thus, the results of scoring the quality of preparation for FCS by the patient and the doctor cannot be considered as interrelated and should be considered separately, taking into account the fundamentally

different subjective approach on the part of the patient and the objective approach of the doctor to assessing the quality of this procedure.

The results of the analysis of the assessment of the quality of preparation for FCS by patients and doctors are presented in Table 1 and Fig. 2.

The results of a study using a modified universal scheme in 30 patients showed the rationality of a differentiated personalized approach to choosing the dose of macrogol (2 l or 2.5-3 l) depending on the nature of the stool in the morning on the day of colonoscopy.

7 patients out of 30 (23%) required only 2 liters of Endofalk solution to achieve adequate quality of preparation; the remaining patients additionally took 0.5-1 liters of the drug in the morning. The proportion of patients who required the maximum dose of the drug (3 l) was 17% (5 patients).

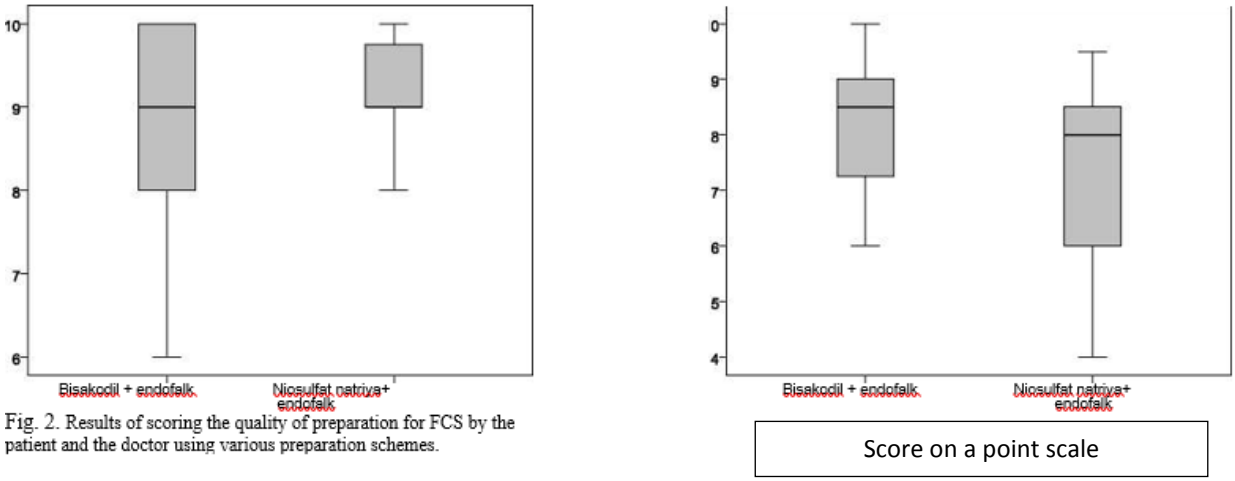

Fig. 2. Results of scoring the quality of preparation for FCS by the patient and the doctor using various preparation schemes.

Among patients using a bisacodyl regimen, only 4 of 15 patients used a single-stage Endofalk regimen (27%, 95% CI: 11-52%), and among patients using a sodium picosulfate regimen, a single-stage Endofalk regimen was used 3 out of 15 patients (20%, 95% CI: 7-45%), while the differences between groups were not statistically significant ($p = 0.500$). In order to reduce the width of the confidence interval, the compared groups were combined. The results of calculating the new confidence interval for the combined group allowed us to draw the following conclusion: patients will use a one-stage regimen of Endofalk in 12-40% of cases (95% probability), while at least 60% of patients will use two a step-by-step scheme (regardless of whether it will be used in combination with bisacodyl or sodium picosulfate).

For clinical assessment of the quality of preparation for FCS by patients and doctors, the obtained scores were transferred to a rank scale, including the following ordinal values:

Low quality of preparation - the range of values is from 0 to 3.3 points.

Average quality of preparation - range of values 3.4 to 6.7 points.

High quality of preparation - range of values 6.8 to 10 points.

According to the results of this ranking analysis of patients' assessment of the quality of preparation for FCS, when using a regimen with bisacodyl, 14 patients (93%) rated the quality of preparation for FCS as high, and only 1 patient (7%) rated the quality of preparation as average . When using a regimen with sodium picosulfate, the quality of preparation for FCS was rated as high by all 15 patients (100%).

But when analyzing the assessment of the quality of preparation for FCS by a doctor, when using both a regimen with bisacodyl and a regimen with sodium picosulfate, the quality of preparation was assessed as high in 12 cases out of 15 (80%).

It should be noted that in the entire observed sample of patients, out of a total of 6 cases of average quality of preparation (as assessed by a physician), 2 cases corresponded to the use of a one-stage scheme. It was found that out of 7 patients who used a one-stage scheme, the quality of preparation

was average in 2 patients (29% of cases), while out of 23 patients who used a two-stage scheme, the quality of preparation was average in only 4 patients (17% of cases). Although there were no statistical differences between the results of using one-stage and two-stage preparation schemes (p = 0.433), the odds ratio of obtaining average rather than high quality of preparation for the FCS when using a one-stage preparation scheme compared to a two-stage preparation scheme is 1. 9, that is, the chances of getting a worse training result are approximately 2 times higher when using a one-stage scheme compared to a two-stage one (according to the results of this study).

It should be noted that the assessment of the quality of preparation for FCS by patients and doctors differs significantly. Patients noted a high quality of preparation for FCS when using a regimen with sodium picosulfate, and doctors, on the contrary, when using a regimen with bisacodyl, although no statistically significant differences were found between these regimens. Taken together, when using regimens with bisacodyl and sodium picosulfate, one can expect that the quality of preparation for FCS will be rated by the doctor as high in 55-92% of cases (95% CI). At the same time, endoscopists noted that when using a two-stage preparation scheme for patients, in 10 out of 23 patients (43%) the presence of transparent liquid contents was determined in the proximal parts of the colon, which did not affect the quality of endoscopy, but required additional medical procedures. During the study, no adverse events associated with the use of the drug "Endofalk" were recorded.

Conclusion. Thus, in this study, personalization of preparation for FCS using Endofalk in combination with bisacodyl or sodium picosulfate contributed to the intake of a significantly smaller amount of fluid (2-3 l) compared to generally accepted regimens, which was a favorable factor for achieving compliance. The results of the study demonstrated the high effectiveness of preparation regimens for FCS using bisacodyl or sodium picosulfate in combination with Endofalk. Based on the results of this study, it can be predicted that at least 60% of patients will use a two-stage regimen for taking Endofalk, both in combination with bisacodyl and in combination with sodium picosulfate. Based on a personalized approach to performing intestinal lavage, we have shown that second-generation PEG preparations can be used not only as mono-preparations for preparation for FCS, but also in combination with laxatives.

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