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ORIGINAL ARTICLE

Pro-motility Preparation Protocol May Reduce the Rates of Failed Patency Capsule Among Patients with Crohn's Disease in Clinical Remission

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Abstract

Background Patency capsule (PC) ingestion is commonly used to minimize capsule retention in high-risk patients with Crohn's disease (CD). However, false-positive rates remain high, precluding the use of video capsule endoscopy (VCE). We aimed to compare the efficacy of two preparation protocols in reducing failed PC rates in patients with CD.

Methods This bi-center retrospective case–control study included adult patients with small-bowel CD in clinical remission who underwent PC ingestion. The pro-motility group followed a low-residue diet, then a clear fluid diet, and took bisacodyl after ingestion, while the control group followed only a clear fluid diet. The primary outcome was failed PC, defined as the absence of PC excretion or presence on abdominal X-ray at 30 h post-ingestion. Multivariable logistic regression was used to identify predictors of failed PC.

Results Among 273 patients (83 in the pro-motility group, 190 controls), the pro-motility group was older (median 36 [27–48] vs. 31 [24–43], $p=0.012$) and had a lower rate of B2/3 disease phenotype (32.5 vs. 53.1%, $p=0.002$) compared to controls. The pro-motility group also had a lower failed PC rate (12.0 vs. 24.7%, $p=0.023$). Longer disease duration (adjusted odds ratio (AOR) 1.053, 95% confidence interval (CI) 1.016–1.091, $p=0.005$) increased the odds of failed PC, while the pro-motility protocol was protective (AOR 0.438, 95% CI 0.200–0.956, $p=0.038$), outweighing the influence of B2/3 disease phenotype (AOR 1.743, 95% CI 0.912–3.332, $p=0.093$).

Conclusions The pro-motility preparation protocol could substantially improve the success rates of the small-bowel patency test in patients with CD undergoing PC ingestion, potentially reducing the risk of capsule retention and associated complications.

Keywords Patency capsule · Failed PC · Bisacodyl · Pro-motility preparation protocol

Introduction

Up to 80% of patients with Crohn's disease (CD) have small bowel (SB) involvement, while exclusive SB involvement is seen in more than 30% of patients [1]. The emerging use of SB capsule endoscopy (SBCE) over the last two decades has enabled the visualization of previously obscured parts of the gastrointestinal tract, leading to more accurate disease diagnoses [2–4]. However, retained SBCE in patients with CD is considered a major adverse event. The SBCE retention rate can reach up to 8.2% without preliminary SB patency confirmation [5–7] and 2.3–4.63% [8, 9] when patency is initially confirmed. Therefore, patency confirmation is highly recommended prior to SBCE ingestion in this population [10, 11].

The patency capsule (PC) is an ingestible capsule with the same shape and size as SBCE but with a self-dissolution mechanism initiating approximately 30 hours post-ingestion, with minimal harmful consequences [12]. Its usefulness has been proven in identifying patients at high risk for retained SBCE [13, 14],and both PC and cross-sectional imaging procedures are equally recommended by both US and European guidelines to preclude this complication (i.e., SBCE retention) in CD [10, 11]. Though PC may have a reduced false-positive (FP) result rate compared to magnetic resonance

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enterography (MRE) for assessing SB patency in CD [15], its reported FP result rates are still quite high (i.e., 55–87%) in patients undergoing the PC procedure prior to SBCE ingestion [16–19].

Upon excretion of the PC in stool, or its absence on abdominal X-ray within 30 hours of ingestion, SB patency is confirmed [12]. Previously published studies have suggested an association between constipation and an increased likelihood of failed PC [16, 17], as well as a significant influence on the likelihood of FP results in failed PC [16]. It is postulated that colonic slow transit may result in a delayed excretion time (i.e., > 30 hours) of PC in patients with constipation, even though SB patency is preserved. Therefore, the use of prokinetics and laxatives as part of bowel preparation in patients undergoing PC may be beneficial in improving PC excretion rates.

Data regarding bowel preparation prior to PC ingestion are scarce, and guidelines in this field area are lacking. In this bi-center study, we aimed to compare two different bowel preparation protocols before and during PC ingestion to reduce the rates of failed PC in patients with CD in clinical remission.

Methods

Study Design and Population

This was a retrospective bi-center case–control study that included adult patients (≥ 18 years old) with established CD in clinical remission (as determined by the treating gastroenterologist during clinic visits) who underwent PC ingestion (Given Imaging, Yoqneam, Israel) prior to SBCE to rule out capsule retention. The study population consisted of patients from two cohorts at two medical centers in Israel. Patients at Sheba Medical Center were part of two prospective studies aiming to monitor mucosal inflammation during clinical remission [20, 21], while patients at Tel-Aviv Sourasky Medical Center underwent PC ingestion as indicated by the treating gastroenterologist, either prior to treatment de-escalation or due to an elevated inflammatory biomarkers during clinical remission. Only patients with SB-CD (L1/L3) in clinical remission were included, while those with exclusive Crohn's colitis (L2) were excluded.

Bowel Preparation Protocols

For the purpose of this study, we utilized the fact that each of the two medical centers regularly follows a different preparation protocol. Patients in the pro-motility group (Tel-Aviv Sourasky Medical Center) followed a low-residue diet for 24 hours starting 48 hours before PC ingestion, followed by a clear-fluid diet for 12 hours, and then fasting for 8–10 hours before ingestion. During capsule ingestion, they were given 10 mg of bisacodyl, taken simultaneously with the PC. Patients in the control group (Sheba Medical Center) adhered to a clear-fluid diet for 6 hours, followed by fasting for 10 hours before PC ingestion. Drinking and eating were resumed 2- and 4-hours post-ingestion, respectively, in both groups.

Study Endpoints

The primary endpoint was defined as failed PC (i.e., the absence of PC excretion in the stool or its presence in the abdomen on abdominal X-ray within 30 hours of ingestion). Secondary endpoints included the need for endoscopic and/or surgical intervention to extract a retained PC, or adverse events following PC ingestion (e.g., obstructive symptoms). Cases of SBCE retention following a passed PC were also documented (i.e., SBCE remaining in the SB for more than 2 weeks, as detected by cross-sectional imaging). The pre-defined endpoints were compared between the study groups (pro-motility vs. control). We also aimed to identify predictors of failed PC in patients with CD in clinical remission.

Data Extraction

Clinico-demographic features were collected via the electronic health records of both medical centers: age, sex, body mass index [BMI] (kg/m^2), current smoking status, disease duration (years), age at diagnosis, anatomic extent and disease phenotype upon referral to SBCE as defined by the Montreal classification [22], perianal involvement, extra intestinal manifestations, prior intestinal operation, current use of biologics, and the presence of elevated inflammatory biomarkers (C-reactive protein [CRP]) > 5 ml/dL and fecal calprotectin [FC] > 250 µg/g).

Statistical Analysis

Categorical variables were described as proportions. Continuous variables were presented as median and interquartile range (IQR) following normality checking by Shapiro–Wilk test. Comparisons between groups were conducted using Mann–Whitney *U* test for continuous variables and fisher exact-test for categorical variables. Multivariable binary logistic regression was applied to identify independent predictors of the primary outcome. For this analysis we included variables which were significant on univariable analysis, and those variables known to be associated with the primary endpoint (i.e., failed PC). Stepwise forward selection-method (likelihood ratio) was performed and $p > 0.1$ was used as criteria for variable removal. Classification and regression tree (CART) [23] analysis was applied in order

to identify subgroups of individuals with increased risk for failed PC. A receiver operating characteristic (ROC) curve was constructed and area under the curve (AUC) was calculated for both logistic regression model and decision tree algorithm to evaluate their diagnostic performance in identifying failed PC event. Odds ratios (OR), adjusted odds ratios (AOR), and area under the curve (AUC) were reported along with their 95% confidence intervals (CI). All statistical tests were 2-sided and $p < 0.05$ was considered as statistically significant. Statistical analyses were conducted using SPSS software (IBM SPSS statistics for windows, version 26, IBM corp. Armonk, NY, USA, 2019).

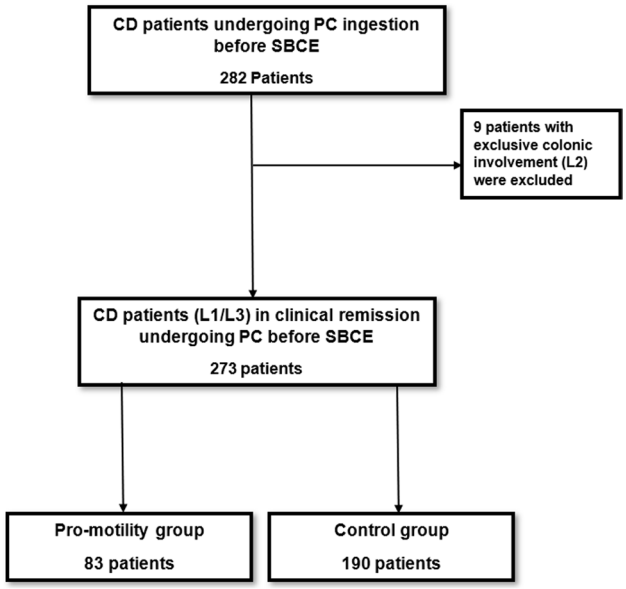

Fig. 1 Study flowchart. Abbreviations: Crohn's disease, CD; small-bowel capsule endoscopy, SBCE; Patency capsule, PC

Results

Patients' Baseline Characteristics

Of 282 patients with CD in clinical remission who underwent the PC procedure (92 from Tel-Aviv Sourasky Medical Center, 190 from Sheba Medical Center), nine patients with exclusive colonic involvement (L2) were excluded. Thus, 273 patients were included in the study cohort (pro-motility group: 83, control group: 190), as shown in Fig. 1. Baseline characteristics of the study cohort are presented in Table 1. Patients in the pro-motility group were older compared to controls (median 36 [27–48] years vs. 31 [24–43] years, $p = 0.012$), while no significant difference was observed in sex prevalence between the groups (males: 54.2 vs. 57.9% in the pro-motility and control groups, respectively, $p = 0.597$). Patients in the pro-motility group had lower rates of colonic involvement (L3) [21.6 vs. 42.3%, $p = 0.001$] and B2/3 disease phenotype (32.5 vs. 53.1%, $p = 0.002$) compared to controls. Biologic treatment was less prevalent in the pro-motility compared to the control group (38.5 vs. 61.1%, $p = 0.001$). The remaining disease-related features, including previous CD-related surgery rates and baseline levels of inflammatory biomarkers, were generally comparable between the groups, as shown in Table 1.

Table 1 Patients' baseline characteristics

	Pro-motility group ($n = 83$)	Control group ($n = 190$)	p-value
Age (years) median (interquartile range)	36 (27–48)	31 (24–43)	0.012
Sex (male) n (%)	45 /83 (54.2%)	110/190 (57.9%)	0.597
Body mass index (kg/m^2) median (interquartile range)	24.22 (21.49–27.18)	23.09 (21.32–25.73)	0.190
Current smoking n (%)*	7/78 (9.0%)	24/187 (12.8%)	0.411
Perianal disease n (%)*	14/83 (16.8%)	31/186 (16.6%)	1.000
Colonic involvement n (%)*	18/83 (21.6%)	80/189 (42.3%)	0.001
Proximal small-bowel involvement n (%)*	6/83 (7.2%)	27/189 (14.2%)	0.111
B2/B3 disease phenotype n (%)*	27/83 (32.5%)	100/188 (53.1%)	0.002
Previous CD-related surgery n (%)*	11/83 (13.2%)	41/189 (21.6%)	0.132
Extra intestinal manifestations n (%)*	14/83 (16.8%)	49/185 (26.4%)	0.090
Age at diagnosis (years) median (interquartile range)	25.0 (20.0–42.0)	24.0 (19.0–34.0)	0.122
Disease duration (years) median (interquartile range)	5.0 (1.0–10.0)	3.3 (1.75–10.0)	0.556
Current biologic use n (%)*	32/83 (38.5%)	82/134 (61.1%)	0.001
Elevated fecal calprotectin level (> 250 µg/mg) n (%)[#]	12/60 (20.0%)	46/149 (30.1%)	0.127
Elevated C-reactive protein level (> 5 mg/dl) n (%)[$]	26/59 (44.0%)	59/189 (31.2%)	0.084

CD Crohn's disease

*Data were missing < 3%, [#]Data were missing < 25%, [$]Data were missing for < 10%

The Rates and Predictors of Failed PC

Failed PC rates were 12.0% (10/83 patients) in the pro-motility group compared to 24.7% (47/190 patients) in the control group ($p=0.023$), as shown in Fig. 2.

In univariable analysis, longer disease duration (OR 1.055, 95% CI 1.020–1.091, $p=0.002$), B2/B3 disease phenotype (OR 2.549 95% CI 1.388–4.681, $p=0.003$) and the pro-motility preparation protocol (OR 0.417, 95% CI 0.199–0.872, $p=0.023$) were associated with failed PC event (Table 2). Upon multivariate logistic regression analysis, longer disease duration (AOR 1.053, 95% CI 1.016–1.091, $p=0.005$) was associated with an increased probability of failed PC, while the use of the pro-motility preparation protocol (AOR 0.438, 95% CI 0.200–0.956, $p=0.038$) was identified as protective against the failed PC event (Fig. 3a).

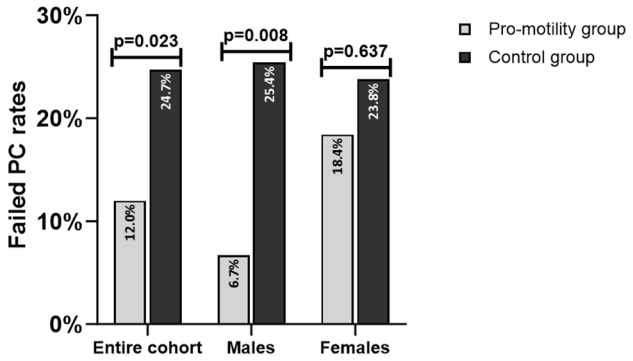

Fig. 2 Failed patency capsule (PC) among the study population

Figure 3b depicts a classification tree algorithm for the failed PC event. The analysis showed that the use of the pro-motility preparation protocol was the most influential factor regarding the probability of failed PC among patients with CD and a disease duration > 7 years (20.0 vs. 40.3% in the pro-motility compared to the control group, respectively, $p=0.096$). Conversely, among patients with CD and a disease duration ≤ 7 years, having a complicated disease phenotype (B2/3) was the most crucial factor associated with the risk of a failed PC event (20.8 vs. 10.1% in patients with B2/3 vs. B1 disease phenotype, respectively, $p=0.051$). Both the logistic regression model and the decision tree algorithm had comparable diagnostic performance in identifying failed PC events (AUC 0.68 vs. 0.67, respectively, $p<0.001$ for both, Fig. 3c).

Sensitivity Analysis

In the subgroup analysis restricted to males ($n=155$), the use of the pro-motility preparation protocol was associated with an 80% reduction in the failed PC rate compared to the controls (6.7 vs. 25.4%, OR 0.209, 95% CI 0.060–0.728, $p=0.008$). However, the failed PC rates were comparable in

Table 2 Univariable and multivariable analyses regarding the probability of failed patency capsule in patients with Crohn's disease (CD) in remission

	Univariable analysis		Multivariable analysis		
	Odds ratio	*p*-value	Adjusted odds ratio	95% Confidence interval	*p*-value
Age (years)[$]	1.011	0.296			
Male sex (vs. female)[$]	0.885	0.764			
Body mass index (kg/m^2)	0.961	0.305			
Current smoking (vs. past/never)	0.532	0.347			
Perianal disease (vs. none)	1.106	0.841			
Colonic involvement (vs. none)	0.949	1.000			
Proximal small-bowel involvement (vs. none)	1.492	0.363			
B2/B3 disease phenotype (vs. B1)[$]	2.549	0.003	1.743	0.912–3.332	0.093
Previous CD-related surgery (vs. none)[$]	1.517	0.258			
Extra intestinal manifestations (vs. none)	0.671	0.373			
Age at diagnosis (years)	0.989	0.337			
Disease duration (years)[$]	1.055	0.002	1.053	1.016–1.091	0.005
Current biologic use (vs. none)[$]	1.859	0.051			
Elevated fecal calprotectin (μg/mg)	2.201	0.069			
Elevated C-reactive protein (mg/dl)	1.675	0.109			
Pro-motility preparation protocol (vs. clear fluid-only protocol)[$]	0.417	0.023	0.438	0.200–0.956	0.038

*> 250 μg/mg [#] > 5 mg/dl. [$]Variables that initially were incorporated into the stepwise forward LR binary logistic regression analysis

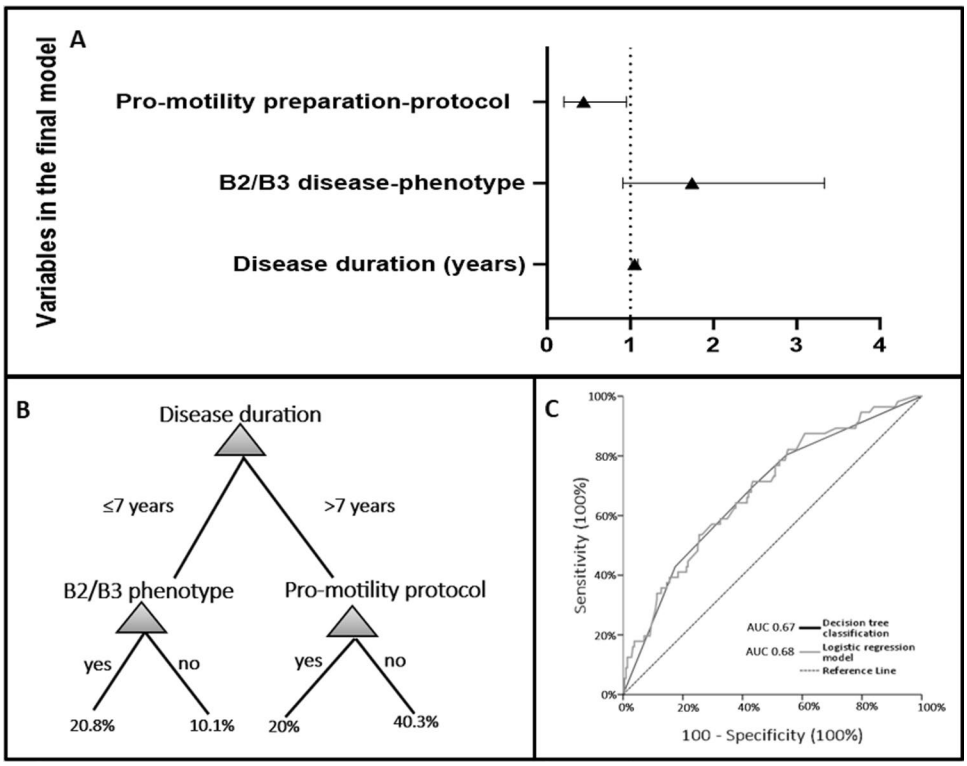

Fig. 3 Multivariable analysis model for failed patency capsule (PC) among patients with Crohn's disease (CD) in clinical remission depicted as Forest plot (**a**). Classification tree algorithm for failed PC among CD patients in clinical remission (**b**). Receiver operating characteristic curve of the diagnostic accuracy of the multivariable logistic regression model and the decision tree algorithm to identify failed PC event in patients with CD in clinical remission (**c**). Abbreviations: AUC; adjusted odds ratio, AOR; confidence interval, CI; area under the curve, AUC

the analysis restricted to females ($n=118$) (18.4 vs. 23.8% in the pro-motility and the control groups respectively, OR 0.725, 95% CI 0.275–1.909, $p=0.637$), as shown in Fig. 2. Baseline characteristics were comparable between males and females in the study cohort, but there was a higher rate of elevated CRP in females compared to males (42 vs. 28%, respectively, $p=0.031$). No significance regarding the pro-motility preparation protocol and the probability of a failed PC was achieved in the analysis restricted to the B2/B3 disease phenotype subgroup (OR 0.353, $p=0.094$).

Safety of Patency Capsule and Capsule Retention Rates

Of the 273 patients undergoing PC ingestion, only one patient with a failed PC in the control group experienced 48 hours of self-limiting mild gastrointestinal symptoms (0.4%). We also observed a single subsequent SBCE retention in the control group, which resolved spontaneously (0.4%). There was no need for any surgical and/or endoscopic intervention or hospitalization in the study cohort following PC ingestion.

Discussion

In this retrospective bi-center study, we compared, for the first time, two different preparation protocols before PC ingestion among patients with CD in clinical remission. We found that in this population, a pro-motility preparation protocol based on a low-residue diet followed by clear fluids and post-capsule-ingestion bisacodyl was superior to a clear fluid-diet alone for reducing the rates of failed PC events and increasing the successful patency test of the SB. Moreover, longer disease duration was associated with an increased risk of failed PC, while the use of the pro-motility preparation protocol prior to and during PC ingestion was associated with more than a 50% reduction in the probability of failed PC in this population, overshadowing other risk factors, including B2/3 disease phenotype and previous CD-related surgery.

Mucosal healing (MH) is a paramount goal in the management of patients with CD, as it has been linked to improved long-term outcomes in this population [24]. In light of the substantial rate of patients with CD who have exclusive SB disease involvement (~30%), the role of SBCE has become crucial in accurately evaluating MH in CD [1]. SBCE has been proven to be a useful tool in diagnosing and monitoring patients with CD and in identifying future disease adverse events, among them [4, 20, 25–27]. However, its use is limited by the potential risk of capsule retention, which may lead to self-limiting mild symptoms or serious complications such as SB obstruction or perforation, resulting in emergent surgery [8]. SB patency confirmation before SBCE ingestion has led to reduced capsule retention rates by 50–70% among patients with established CD [5–9]. Therefore, both US and European guidelines endorse

the assessment of SB patency prior to SBCE ingestion in patients with CD [10, 11].

The use of PC in patients with CD has been proven to accurately screen out patients at high risk for retained SBCE [13, 14], and it has a higher negative predictive value (NPV) compared to MRE in assessing SB patency in CD[15]. We also demonstrated its predictive yield for future adverse events in patients with quiescent CD [28]. Yet, the PC procedure has a considerable rate of FP results (i.e., 55–87%) among patients undergoing the procedure before SBCE for any reason (i.e., CD assessment and diagnosis, gastrointestinal bleeding, polyp follow-up, etc.) [16–19], leading to insufficient positive predictive value (PPV) for evaluating SB patency [16–19]. Previously published studies found a non-significant association between constipation and failed PC [16, 17]. However, in an analysis restricted to patients with FP results of failed PC ($n=24$), constipation was the only factor that independently increased the probability of failed PC (OR 13.858, $p=0.042$) [16], while it had no influence on SB patency confirmation based on a two-step assessment process (i.e., PC ingestion → cross-sectional imaging) [16, 18]. It is, therefore, conceivable that PC excretion time might be delayed (≤ 72 h) and still represent intact SB patency [13].

Notably, in our study, colonic involvement was more prevalent in the control group compared to the pro-motility group. Colonic disease involvement in CD can result in either diarrhea [29] due to inflamed mucosa or constipation with delayed transit time due to colonic strictures [30], which may hinder PC excretion in these patients. However, no association between colonic disease involvement and the risk of failed PC was demonstrated. Unfortunately, data regarding bowel movement habits in the cohort population were unavailable, limiting our understanding of the impact of colonic involvement on PC results.

In our study, we observed that patients with CD in clinical remission who followed the pro-motility preparation protocol had a lower rate of failed PC compared to controls who followed the fluid-only preparation protocol. This finding contrasts with a previously published study, which found no association between the use of prokinetics and the likelihood of failed PC among patients who underwent PC ingestion for any indication [16]. However, practical conclusions from that study were limited by the low prevalence of prokinetic use in its study population (5.67%) [16]. Interestingly, we found that the pro-motility preparation protocol has a stronger and more significant effect on males (OR 0.209, $p=0.008$) compared to females (OR 0.725, $p=0.637$). This observation may be explained by the higher prevalence and greater severity of constipation in females compared to males [31]. Considering the above-mentioned findings and the generally comparable baseline characteristics between females and males in our study, these results may indicate the need for a more robust preparation protocol for female patients. Our findings suggest the need for further research to tailor preparation protocols to distinct sub-populations in CD to reduce the rates of failed PC in CD.

Longer disease duration in patients with CD is associated with higher rates of complicated disease phenotypes, progressing from B1 to B2/B3 phenotypes over time [32]. It therefore reasonable that longer disease duration might be associated with an increased risk of failed PC, as demonstrated in our study. Not surprisingly, in the analysis restricted to patients with B2/B3 disease phenotypes, the use of pro-motility preparation protocol did not improve failed PC rates in this population, likely indicating an anatomical rather than motility-related cause for a failed PC event.

Consistent with the existing literature, we found PC ingestion to be a tolerable and safe procedure, with only one patient experiencing self-limiting mild symptoms following the procedure. Abdominal pain after PC ingestion was reported in 2/326 patients (~0.6%) in a recently published study [17]. Older studies reported higher rates (10–22%) of abdominal pain following PC ingestion; however, in most of those studies, patients had a prior history of symptomatic strictures, unlike the patients in our cohort who were in clinical remission. Our study further strengthened the value of the PC procedure in preventing SBCE retention. We observed only a single case of SBCE retention following a failed PC result (0.4%), which was consistent with the reported rates (0.39–2.1%) [12, 16, 18] of this complication in patients with confirmed SB patency by PC. In contrast, the reported rates of capsule retention were much higher in patients with a failed PC result (11.1%) [12].

This study had several limitations, primarily due to its retrospective design. First, there were no data regarding bowel movements, exercise habits, or daily fluid intake among the study population, which might have influenced PC passage through the SB. However, the cohort was relatively homogenous, consisting of adult patients with CD in clinical remission. Second, the unbalanced higher rate of B2/3 disease phenotype in the control group, along with the higher median age in the pro-motility group compared to the control group, may have influenced the observed failed PC rates. However, in a logistic regression analysis incorporating both variables among others, the use of the pro-motility preparation protocol was still independently associated with a reduced likelihood of a failed PC event. Finally, no cross-sectional imaging was performed following PC ingestion among the study patients, so we could not assess the true FP rates of failed PC or how these rates were affected by the pro-motility preparation protocol. Moreover, cross-sectional imaging is not typically performed following a failed PC event in real-life practice for patients with CD, and there are no guidelines to endorse this approach.

In conclusion, in this bi-center study, we compared, for the first time, two different preparation protocols before PC ingestion among patients with CD in clinical remission. The failed PC rates were significantly lower with the pro-motility preparation protocol, which included a low-residue diet, fluid diet, and bisacodyl, compared to a clear fluid-only diet. Furthermore, longer disease duration was associated with an increased risk of failed PC, while the use of the pro-motility preparation protocol was associated with a decreased likelihood of a failed PC event. Therefore, the pro-motility preparation protocol should be considered prior to PC ingestion in patients with CD in remission to reduce failed PC rates in this population. Further research with a larger cohort is needed to explore this observation more thoroughly and to tailor bowel preparation protocols more effectively for distinct populations with CD.

Author's contributions OU, LD, and UK conceived the study and participated in study design. EN and LD developed the pro-motility preparation protocol. OU drafted the manuscript and participated in data analysis. LD participated in drafting of the manuscript. AD and ML participated in data analysis. OU, AD, TB, ATA, TT, AH, NM, EN, ML, RE, SBH, UK and LD participated in acquisition of data, in data interpretation and in critical revision of the manuscript for important intellectual property. All authors have approved the final draft submitted.

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Data availability statement The data underlying this article will be shared on reasonable request to the corresponding authors.

Declarations

Conflict of interest Shomron Ben-Horin has received Advisory board and/or consulting fees from Abbvie, Takeda, Janssen, Celltrion, Pfizer, GSK, Ferring, Novartis, Roche, Gilead, NeoPharm, Predicta Med, Galmed, Medial Earlysign, BMS and Eli Lilly, holds stocks/options in Predicta Med, Evinature & Galmed, and received research support from Abbvie, Takeda, Janssen, Celltrion, Pfizer, & Galmed. Uri Kopylov received speaker and advisory fees: Abbvie, BMS, Celtrion, Janssen, Medronic, Pfizer, Roche, Takeda, Elly Lili, research support: Janssen, Medtronic, Takeda, Elly Lili Abbvie BMS. Rami Eliakim received consultant and speaker fees from Janssen, Abbvie, Takeda and Medtronic. Eva Niv received consultant fees from Medtronic. Nitsan Maharshak has received speaking and/ or consulting fees from Pfizer, Abbvie, Lilly, Takeda, Janssen, Ferring, BiomX, BMS, Nestle, Trobix Innovation, Teva and grant support from Takeda, Janssen, Abbott, Abbvie, Pfizer, BMS, Corundum Innovation Ltd, Nestle. Ayal Hirsch has received speaking honoraria from Perigo, Padagis, Janssen, Abbvie, Takeda and received grants from Janssen, Takeda and Abbvie. Tamar Thurm has received lecture fee from Takada. Liat Deutsch has previously received payment for consulting and/or lecturing services from Medtronic, Neopharm, Abbott, Abbvie, and Fresenius Kabi. The remaining authors (Offir Ukashi, Arad Dotan, Tom Borkovsky, Adi Talan Asher, Moshe Leshno) declare that they have no conflicts of interest.

Ethical approval This study was carried out in accordance with the ethical guidelines of the Declaration of Helsinki. The study was approved by the Sheba Medical Center ethics committee and the Tel-Aviv Sourasky Medical Center ethics committee. Approval was granted for Helsinki protocol SMC-13-0218 (July 2nd, 2013), SMC-18-4945 (June 26th, 2018) and TLV-0032-23 (March 26th, 2023) and TLV-0292-19 TLV-0292-19 (Sep. 4th, 2019). Since this was a retrospective case–control study, no informed consent was obtained for this specific analysis. However, informed consent was obtained from patients who were part of the prospective cohorts of this study.

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