Research Square

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Pre-procedure 600 mg Simethicone Maintains Bowel Preparation Quality and Yields Higher Adenoma Detection: A Four-arm, Assessor-blinded Randomized Trial

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Abstract

Background and aims: We evaluated whether 600 mg simethicone before colonoscopy could maintain bowel preparation quality while improving adenoma detection and tolerability compared with 1,200 mg, and whether administration immediately or 1 hour after completion of split-dose polyethylene glycol modified these outcomes.

Methods: This prospective, single-center, assessor-blinded, four-arm randomized trial included 1,111 adults who completed colonoscopy after split-dose 3-L polyethylene glycol. In a 2-by-2 factorial design, groups A and C received 600 mg simethicone immediately or 1 hour after polyethylene glycol, respectively, followed by 600 mg after returning to the ward; groups B and D received 1,200 mg immediately or 1 hour after polyethylene glycol, respectively. The primary outcome was the overall 0-3 bubble score recorded before flushing or suction. Secondary outcomes were total and segmental Boston Bowel Preparation Scale (BBPS) scores, adequate preparation, procedural withdrawal time, adenoma detection rate (ADR), and common adverse events. Dose, timing, and dose-by-timing interaction effects were examined. ADR was evaluated with modified Poisson regression using robust standard errors.

Results: Groups A-D included 277, 278, 281, and 275 participants, respectively, with broadly comparable baseline characteristics. Bubble-score distributions did not differ among the four groups (P=0.288), and total BBPS, segmental BBPS, adequate preparation, and procedural withdrawal time were also comparable. ADR was 33.6%, 28.1%, 37.7%, and 28.4% in groups A-D, respectively (global P=0.042). When the factorial dose levels were combined, ADR was significantly higher after 600 mg than after 1,200 mg before colonoscopy (35.7% vs 28.2%; absolute difference, 7.5 percentage points). After adjustment for age, sex, indication, and family history of gastrointestinal cancer, the adjusted risk ratio was 1.253 (95% CI 1.054-1.490; P=0.010). Administration timing was not associated with ADR, and no dose-by-timing interaction was observed. Abdominal pain (9.3% vs 13.4%), bloating (10.6% vs 14.6%), nausea (2.9% vs 5.2%), and vomiting (1.1% vs 2.7%) were less frequent in the 600-mg arms.

Conclusions: With split-dose 3-L polyethylene glycol, 600 mg simethicone before colonoscopy provided bubble control and bowel cleansing comparable to 1,200 mg, while yielding a significantly higher ADR and lower rates of common adverse events. The 600-mg regimen offers a favorable balance of preparation quality, lesion detection, and tolerability.

Introduction

Colorectal cancer commonly develops through an adenoma-carcinoma sequence, making the detection and removal of precursor lesions a central objective of screening and surveillance colonoscopy. The preventive benefit of colonoscopy depends not only on cecal intubation, but also on complete mucosal exposure and careful inspection during withdrawal. Adenoma detection rate (ADR), defined as the proportion of examinations in which at least one adenoma is identified, is therefore a key colonoscopy quality indicator. Higher endoscopist ADRs are associated with lower risks of interval colorectal cancer

and colorectal cancer-related death [1–3]. Interventions that preserve mucosal visibility and facilitate lesion recognition may consequently have direct value for colonoscopy quality improvement.

Effective bowel preparation requires control of solid residue, residual fluid, and intraluminal bubbles. The Boston Bowel Preparation Scale (BBPS) provides a validated assessment of cleansing in the right, transverse, and left colon after washing and suction [4]. An examination may nevertheless meet accepted BBPS thresholds while small or confluent bubbles continue to cover portions of the mucosal surface. Such bubbles can interfere with visualization between folds and may make flat or diminutive lesions more difficult to recognize. Suboptimal mucosal visualization has been associated with substantial adenoma miss rates on early repeat colonoscopy [5]. Bubble control is therefore a distinct component of preparation quality that is not fully represented by post-cleansing BBPS scores.

Simethicone is a nonabsorbed surfactant that lowers surface tension, allowing small gas bubbles to coalesce and disperse. It is widely used as an adjunct to oral bowel preparation, and both European and US guidance recognize its role in improving intraluminal visibility [6, 7]. Randomized trials spanning different polyethylene glycol volumes and clinical settings consistently show reductions in bubble burden and irrigation requirements [8–15]. Meta-analyses confirm the defoaming benefit, although reported effects on BBPS, procedural efficiency, and ADR remain heterogeneous [16–18]. Differences in purgative regimens, simethicone dose, timing of administration, and outcome assessment may account for part of this variation.

Evidence from direct dose comparisons has not established a consistent advantage of 1,200 mg over lower-dose simethicone when polyethylene glycol is used [19, 20]. This pattern raises the possibility that clinically useful defoaming is achieved at a lower dose and that further dose escalation provides limited incremental benefit. In addition, the interval between completion of polyethylene glycol, simethicone administration, and colonoscopy may influence drug distribution and contact with residual luminal fluid [21, 22]. We therefore conducted a four-arm factorial study crossing two pre-procedure doses, 600 mg and 1,200 mg, with administration immediately or 1 hour after completion of the morning polyethylene glycol. All groups received 1,200 mg across the complete peri-procedural period. The study compared the four regimens and evaluated the effects of pre-procedure dose, administration timing, and their interaction on bubble burden, bowel cleansing, procedural withdrawal time, adenoma detection, and tolerability.

Methods

Study design, setting, and ethics

This prospective, single-center, assessor-blinded, four-arm randomized clinical trial was conducted in the Department of Gastroenterology of Zhongda Hospital, Southeast University, a tertiary hospital in Nanjing, China, between May 2021 and January 2023. The protocol evaluated two pre-procedure simethicone doses at two administration times within a standardized split-dose polyethylene glycol regimen. The

institutional ethics committee of Zhongda Hospital, Southeast University, approved the study (2021ZSSYLL083-P01), and all participants provided written informed consent before study procedures. The trial was prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2100047929). This study was reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Participants

Adults aged 18-70 years who were scheduled for elective colonoscopy were eligible if they were able to understand the study, provide informed consent, and complete the prescribed bowel-preparation regimen. Exclusion criteria were myocardial infarction within the preceding 6 months; severe cardiac, pulmonary, neurologic, or renal disease; known or suspected intestinal obstruction; chronic constipation; previous surgery for colorectal cancer; pregnancy or lactation; hypersensitivity to simethicone, sorbitol, or related formulation components; and participation in another clinical study within 60 days. These criteria identified participants who could safely complete split-dose 3-L polyethylene glycol and the assigned simethicone regimen.

Randomization and blinding

Participants were assigned to groups A-D using an investigator-generated random-number table, as specified in the registered protocol. The participant-level database retained the assigned four-arm code, and the final groups were closely balanced in size. Because the regimens differed in administered volume and timing, participants and staff who provided the bowel-preparation medication were not blinded. Endoscopists who performed the examinations and assigned the bubble and BBPS scores were not informed of treatment allocation, preserving blinded assessment of the principal preparation outcomes.

Bowel preparation and intervention groups

All participants received the same split-dose 3-L polyethylene glycol electrolyte solution regimen in accordance with Chinese bowel-preparation guidance [23,24]. They followed a low-residue diet on the day before colonoscopy and fasted on the day of the procedure. The first 1 L of polyethylene glycol was consumed at 19:00 on the evening before colonoscopy, and the remaining 2 L were completed 4-6 hours before the procedure. Standardizing the purgative, total volume, dietary preparation, and dosing interval allowed the simethicone dose and administration time to be evaluated within a common bowel-cleansing framework.The study nurses who administered the bowel preparation solutions and simethicone were trained according to a standardized protocol.

Simethicone oral emulsion (Berlin-Chemie AG, Germany; 1,200 mg per 30 mL) was administered according to the four regimens shown in Table 1. Group A received 15 mL (600 mg) immediately after completing polyethylene glycol and another 15 mL immediately after returning to the ward following colonoscopy. Group B received 30 mL (1,200 mg) immediately after completing polyethylene glycol. Group C received 15 mL (600 mg) 1 hour after completing polyethylene glycol and another 15 mL after returning to the ward. Group D received 30 mL (1,200 mg) 1 hour after completing polyethylene glycol. Thus, the design crossed pre-procedure dose (600 vs 1,200 mg) with administration timing (immediate vs 1 hour later), while maintaining a total peri-procedural simethicone dose of 1,200 mg in all four groups.

For outcomes measured during colonoscopy, including bubble score, BBPS, procedural withdrawal time, and ADR, groups A and C constituted the 600-mg pre-procedure dose level and groups B and D constituted the 1,200-mg dose level. The additional 600 mg received by groups A and C after colonoscopy was not part of the exposure relevant to these intra-procedural outcomes. The factorial analysis therefore estimated a pre-procedure dose effect of 600 versus 1,200 mg and a timing effect of 1 hour later versus immediately after polyethylene glycol.

Outcomes

The primary outcome was the overall intraluminal bubble score, recorded by the blinded endoscopist during withdrawal before flushing or suction. The ordinal scale ranged from 0 to 3: 0 indicated no or almost no bubbles and an unobstructed mucosal view; 1 indicated a small number of bubbles with a clear view; 2 indicated bubbles occupying approximately one-third to two-thirds of the field; and 3 indicated bubbles occupying more than two-thirds of the field and requiring irrigation [25]. Higher scores represented a greater bubble burden and poorer initial mucosal visibility. Assessment before washing or suction was intended to capture the pre-procedure defoaming effect of oral simethicone.

Secondary outcomes included total BBPS and BBPS scores for the right, transverse, and left colon after cleansing; adequate bowel preparation; procedural withdrawal time; and ADR. Preparation was considered adequate when all three segmental BBPS scores were at least 2. Procedural withdrawal time was measured from the start of withdrawal at the cecum or terminal ileum until removal of the colonoscope at the anus and included time spent on polypectomy or other endoscopic intervention. ADR was defined as the proportion of participants in whom at least one pathologically confirmed adenoma was identified. The database also recorded whether an adenoma was detected in the left, transverse, and right colon, allowing segment-level detection patterns to be compared across regimens.

Tolerability outcomes were abdominal pain, bloating, nausea, and vomiting during the specified observation period. Events were summarized by randomized arm and by the combined pre-procedure dose levels. Groups A and C received their second 600-mg dose after colonoscopy during this period; consequently, the adverse-event comparison described the tolerability of the complete peri-procedural regimens.

Outcome hierarchy and sample size

The overall bubble score was the sole primary outcome and formed the basis of the original sample-size calculation. Study records specified an intended allocation of approximately 278 participants per group, corresponding to a total target of about 1,112 participants. The achieved group sizes ranged from 275 to 281 and closely matched the planned allocation. Total and segmental BBPS, adequate preparation, procedural withdrawal time, overall and segment-level ADR, and adverse events were analyzed as secondary outcomes.

Data quality and statistical analysis

The final database contained 1,111 participants who completed colonoscopy. Data quality checks examined demographic variables, treatment allocation, and internal consistency of the recorded outcomes. Age was missing for two participants. One group-A record contained BBPS values outside the permitted range, with a left-colon score of 6 and a total score of 11. The left-colon and total BBPS values for that participant were therefore treated as missing, while the remaining valid outcomes were retained. For all other participants, total BBPS equaled the sum of the three segmental scores.

Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, according to their distributions; categorical variables were reported as counts and percentages. Because the 0-3 bubble score was ordinal, the primary analysis compared its complete distribution across groups A-D using the Kruskal-Wallis test. Proportional-odds models were then used to estimate pre-procedure dose, administration timing, and dose-by-timing interaction effects on the odds of a worse bubble-score category.

Total and segmental BBPS and procedural withdrawal time were summarized by randomized group and compared with rank-based tests. Binary outcomes, including adequate preparation and ADR, were compared with chi-square tests for the four-group analyses. Factorial models estimated the main effects of 600 versus 1,200 mg and administration 1 hour later versus immediately, together with the corresponding interaction. Procedural withdrawal time was log-transformed for model-based analysis to reduce distributional skew, and between-group effects were expressed as geometric mean ratios.

ADR was analyzed using modified Poisson regression with robust standard errors to obtain directly interpretable risk ratios [26]. The multivariable model included pre-procedure dose, administration timing, age, sex, colonoscopy indication, and family history of gastrointestinal cancer; post-polypectomy surveillance was retained as a separate indication category. The dose-by-timing interaction was tested before the main-effects model was interpreted. Because the interaction was not significant, adjusted dose and timing effects were reported from the additive model. A sensitivity model additionally included the recorded comorbidities to assess the stability of the ADR estimate. Adverse events were compared between the combined 600-mg and 1,200-mg pre-procedure dose groups. All analyses were performed using R version 4.5.2, with two-sided P values below 0.05 considered statistically significant.

Results

Participants and baseline characteristics

A total of 1,200 patients were assessed for participation. Fifty-six did not meet the eligibility or bowel-preparation requirements, and 33 did not complete colonoscopy. The final complete-colonoscopy cohort therefore comprised 1,111 participants, representing 92.6% of the patients initially assessed. Group A included 277 participants, group B 278, group C 281, and group D 275, producing four closely balanced analysis groups (Figure 1).

Baseline age, sex, colonoscopy indication, and most recorded comorbidities were broadly comparable across the four groups (Table 2). Maximum pairwise standardized differences were small for most characteristics. The largest values were 0.201 for prior malignancy and 0.198 for cardiac disease or arrhythmia. Both characteristics were included in the expanded ADR sensitivity model to evaluate whether these modest baseline differences influenced the estimated dose effect.

Primary outcome: bubble score

All four simethicone regimens produced low overall bubble scores. Mean scores were 0.567 (SD 0.504) in group A, 0.651 (SD 0.813) in group B, 0.509 (SD 0.508) in group C, and 0.611 (SD 0.870) in group D. Comparison of the complete ordinal distributions showed no significant difference among the four groups (Kruskal-Wallis P=0.288; Table 3 and Figure 2).

The factorial analysis yielded a consistent result. The odds of being classified in a worse bubble-score category were similar after 600 mg and 1,200 mg before colonoscopy (odds ratio for 600 mg vs 1,200 mg, 1.080; 95% CI 0.858-1.361; P=0.512). Administration 1 hour later rather than immediately after polyethylene glycol was not associated with the bubble-score distribution, and the dose-by-timing interaction was not significant (Table 4).

BBPS and procedural withdrawal time

Mean total BBPS values ranged from 6.37 to 6.53 across the four groups (global P=0.293). Adequate preparation was achieved in 85.6%-91.3% of participants (global P=0.178). Scores for the right, transverse, and left colon were also similar across regimens. Factorial analyses showed no consistent main effect of dose or administration timing and no dose-by-timing interaction for total or segmental BBPS or adequate preparation.

Median procedural withdrawal times were 378 seconds in group A, 354 seconds in group B, 379 seconds in group C, and 380 seconds in group D. Withdrawal time was comparable across the four regimens (global P=0.694), and neither the dose nor timing factor produced a consistent difference in the factorial model.

Adenoma detection

Adenoma detection differed across the randomized groups. ADR was 33.6% in group A, 28.1% in group B, 37.7% in group C, and 28.4% in group D (global P=0.042; Table 3 and Figure 3). At both administration times, the 600-mg group had a higher ADR than the corresponding 1,200-mg group: group A exceeded group B after immediate administration, and group C exceeded group D after administration 1 hour later. When the factorial dose levels were combined, 199 of 558 participants in the 600-mg arms had at least one adenoma detected, compared with 156 of 553 in the 1,200-mg arms. The corresponding ADRs were 35.7% and 28.2%, an absolute difference of 7.5 percentage points.

The ADR difference remained significant in the multivariable analysis. After adjustment for age, sex, colonoscopy indication, and family history of gastrointestinal cancer, the adjusted risk ratio for 600 mg versus 1,200 mg was 1.253 (95% CI 1.054-1.490; P=0.010; Table 5). Thus, the adjusted probability of detecting at least one adenoma was 25.3% higher in the 600-mg arms. Administration 1 hour later rather than immediately was not associated with ADR (adjusted risk ratio, 1.068; 95% CI 0.901-1.266; P=0.446), and the dose-by-timing interaction was not significant (P=0.677). Additional adjustment for the recorded comorbidities produced a similar estimate for 600 mg versus 1,200 mg (risk ratio, 1.242; 95% CI 1.046-1.475).

Segment-level analyses showed the same directional pattern. Compared with the combined 1,200-mg arms, the combined 600-mg arms had numerically higher ADRs in the left, transverse, and right colon (Supplementary Table S2). The higher overall ADR in the 600-mg arms was therefore accompanied by higher detection across multiple colonic segments rather than being confined to a single anatomical region.

Adverse events

All four recorded gastrointestinal adverse events were less frequent in the 600-mg pre-procedure arms than in the 1,200-mg arms. Abdominal pain occurred in 9.3% versus 13.4% (P=0.033), bloating in 10.6% versus 14.6% (P=0.041), nausea in 2.9% versus 5.2% (P=0.045), and vomiting in 1.1% versus 2.7% (P=0.045), respectively (Supplementary Table S1). The direction of the difference was consistent across all four tolerability outcomes.

Discussion

This prospective four-arm trial produced three complementary findings. First, 600 mg and 1,200 mg simethicone before colonoscopy provided comparable control of intraluminal bubbles, total and segmental BBPS scores, and rates of adequate bowel preparation. Second, ADR was significantly higher with the 600-mg pre-procedure dose: 35.7% versus 28.2%, corresponding to an absolute increase of 7.5 percentage points and a 25.3% higher adjusted probability of detecting at least one adenoma. Third, abdominal pain, bloating, nausea, and vomiting were consistently less frequent in the 600-mg arms.

Taken together, these findings indicate that the 600-mg regimen achieved a more favorable balance of preparation quality, lesion detection, and gastrointestinal tolerability.

Bubble score and BBPS characterize different aspects of bowel preparation. The bubble score captures intraluminal foam before washing or suction, whereas BBPS evaluates the segmental mucosal view after cleansing maneuvers. The absence of a dose difference in either measure indicates that 600 mg was sufficient to support stable mucosal visualization within this split-dose 3-L polyethylene glycol regimen. Increasing the pre-procedure dose to 1,200 mg did not improve overall bubble burden, BBPS, or adequate preparation. This finding is consistent with randomized dose comparisons in which higher simethicone doses did not confer a reproducible improvement in bowel-cleansing quality when combined with polyethylene glycol [19, 20]. The collective evidence supports a dose-response plateau: once an effective surfactant concentration is reached, additional simethicone may provide limited incremental improvement in conventional preparation scores.

The ADR difference was the most clinically relevant distinction between the dose levels. The 600-mg advantage was observed at both administration times, remained statistically significant after adjustment for age, sex, examination indication, and family history of gastrointestinal cancer, and was preserved in the expanded sensitivity model. Moreover, segment-level detection was higher in the 600-mg arms in the left, transverse, and right colon. These convergent results strengthen the internal consistency of the overall ADR finding. An absolute difference of 7.5 percentage points is directly relevant to colonoscopy quality because it represents additional participants in whom a precancerous lesion was recognized during the current examination.

Prior randomized studies have reported variable effects of simethicone on adenoma detection. Some trials found higher overall, proximal, or right-colon detection after simethicone supplementation, whereas others observed improved bubble control without a change in overall ADR [11–15]. The present trial extends this evidence by directly comparing two pre-procedure dose levels within the same polyethylene glycol regimen. The higher ADR with 600 mg at both administration times indicates that increasing the dose to 1,200 mg did not provide an additional detection advantage.

Comparable bubble and BBPS scores alongside different ADRs also illustrate that standard preparation scales and lesion detection do not measure identical features of examination quality. BBPS primarily records macroscopic mucosal exposure after cleaning, while a single 0–3 bubble score compresses a complex luminal environment into four categories. The distribution of fine bubbles, the physical characteristics of mucus and residual fluid, transient views behind folds, and the need for repeated irrigation may affect recognition of small lesions without producing a detectable change in an overall score. The present findings therefore show that the practical performance of a preparation regimen may be better reflected by lesion detection than by small differences in conventional cleansing scores alone. Clinical data similarly show that good and excellent preparations can produce comparable overall ADRs even when the detection of advanced adenomas and sessile serrated lesions differs [27].

Administration timing did not materially influence bubble score, BBPS, procedural withdrawal time, or ADR, and the dose-by-timing interaction was not significant. The higher ADR associated with 600 mg was present after both immediate and 1-hour delayed administration. This result suggests that, within the time window studied, pre-procedure dose was more informative than the exact interval after completion of polyethylene glycol. Clinical services may therefore schedule simethicone immediately or 1 hour later according to patient flow and nursing workflow without compromising preparation quality. The lower rates of abdominal pain, bloating, nausea, and vomiting further support the 600-mg strategy. Because groups A and C received the remaining 600 mg after colonoscopy, these adverse-event comparisons describe the tolerability of the complete peri-procedural regimens; the consistently lower event rates nevertheless add to the overall clinical advantage of the lower pre-procedure dose.

The study has several strengths. Its prospective four-arm factorial design allowed dose, administration timing, and their interaction to be evaluated within the same trial. The large complete-colonoscopy cohort and near-equal group sizes provided stable estimates, while use of a common split-dose 3-L polyethylene glycol regimen limited variation in the underlying bowel preparation. Blinded assessment by the endoscopists strengthened the evaluation of bubble score and BBPS, and the multivariable and sensitivity analyses produced closely aligned ADR estimates. The study was conducted at a single center, and the available database did not contain endoscopist identifiers or detailed information on adenoma number, size, or advanced histology. Further multicenter studies can determine whether the observed ADR advantage extends across endoscopists and to advanced neoplasia. The current results nevertheless provide a coherent body of evidence supporting the effectiveness, detection performance, and tolerability of the 600-mg regimen.

Conclusion

Within a split-dose 3-L polyethylene glycol regimen, 600 mg simethicone before colonoscopy achieved bubble control, BBPS, and adequate preparation comparable to 1,200 mg, while producing a significantly higher ADR and lower rates of abdominal pain, bloating, nausea, and vomiting. Administration immediately or 1 hour after completion of polyethylene glycol produced similar colonoscopy outcomes. Considering preparation quality, lesion detection, and tolerability together, 600 mg represents a clinically advantageous pre-procedure simethicone dose.

Declarations

Ethics approval and consent to participate:

Approved by the Zhongda Hospital ethics committee (2021ZSSYLL083-P01). All participants provided written informed consent.

Consent for publication:

Not applicable.

Competing interests:

The authors declare no competing interests.

Trial registration and protocol

The abridged trial protocol can be accessed at the Chinese Clinical Trial Registry (ChiCTR2100047929).

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Author Contribution

Jinxia Chen conceived and designed the study. Yan Ren and Yuanyuan Li managed project administration. Jinxia Chen, Yanyan Meng, Tingting Lu, and Yuanyuan Li collected, organized, and analysed the data. Jinxia Chen drafted the manuscript, and Zhi Wang critically revised it for important intellectual content. All authors approved the final version and agree to be accountable for the work.

Data Availability

The de-identified analysis data are held by the study team. Access is subject to institutional and ethics requirements.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2100047929,registered on 2021-06-27.URL:https://www.chictr.org.cn/showproj.html?proj=ChiCTR2100047929

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Tables

Table 1. Simethicone intervention groups

Arm	n	Timing after PEG	Before colonoscopy	After return to ward	Total peri-procedural dose
A	277	Immediately	15 mL (600 mg)	15 mL (600 mg)	30 mL (1,200 mg)
B	278	Immediately	30 mL (1,200 mg)	None	30 mL (1,200 mg)
C	281	1 hour later	15 mL (600 mg)	15 mL (600 mg)	30 mL (1,200 mg)
D	275	1 hour later	30 mL (1,200 mg)	None	30 mL (1,200 mg)

Note. PEG, polyethylene glycol. The dose after return to the ward was administered after colonoscopy and could not affect intra-procedural outcomes.

Table 2. Baseline characteristics of the complete-colonoscopy cohort

Characteristic	A (n=277)	B (n=278)	C (n=281)	D (n=275)	Maximum pairwise SMD
Age, years	51.1 ± 12.0	52.2 ± 9.2	52.3 ± 11.1	51.8 ± 8.9	0.109
Male sex	148 (53.4%)	152 (54.7%)	149 (53.0%)	139 (50.5%)	0.083
Indication					
Symptom investigation	196 (70.8%)	190 (68.3%)	194 (69.0%)	194 (70.5%)	0.052
Routine health check	43 (15.5%)	46 (16.5%)	36 (12.8%)	42 (15.3%)	0.106
Post-polypectomy surveillance	20 (7.2%)	17 (6.1%)	30 (10.7%)	24 (8.7%)	0.165
Other tumour screening/monitoring	11 (4.0%)	7 (2.5%)	13 (4.6%)	6 (2.2%)	0.135
Inflammatory bowel disease	4 (1.4%)	10 (3.6%)	5 (1.8%)	7 (2.5%)	0.138
Other	3 (1.1%)	8 (2.9%)	3 (1.1%)	2 (0.7%)	0.162
Hypertension	70 (25.3%)	72 (25.9%)	70 (24.9%)	58 (21.1%)	0.114
Diabetes	22 (7.9%)	21 (7.6%)	22 (7.8%)	19 (6.9%)	0.039
Cerebrovascular disease	11 (4.0%)	11 (4.0%)	12 (4.3%)	15 (5.5%)	0.071
Cardiac disease/arrhythmia	8 (2.9%)	17 (6.1%)	14 (5.0%)	6 (2.2%)	0.198
Prior malignancy	7 (2.5%)	10 (3.6%)	14 (5.0%)	4 (1.5%)	0.201
Chronic liver disease	6 (2.2%)	13 (4.7%)	11 (3.9%)	16 (5.8%)	0.187
Family history of GI cancer	8 (2.9%)	9 (3.2%)	6 (2.1%)	8 (2.9%)	0.068

Note. Values are mean ± SD or n (%). SMD, standardized mean difference; GI, gastrointestinal. The final column is the largest absolute SMD among the six pairwise arm comparisons.

Table 3. Primary and secondary outcomes by randomized arm

Outcome	A	B	C	D	Global P value
Bubble score, mean ± SD	0.567 ± 0.504	0.651 ± 0.813	0.509 ± 0.508	0.611 ± 0.870	0.288
Bubble score, median [IQR]	1.0 [0.0-1.0]	0.0 [0.0-1.0]	1.0 [0.0-1.0]	0.0 [0.0-1.0]	0.288
Total BBPS, mean ± SD	6.49 ± 0.86	6.37 ± 0.87	6.53 ± 0.93	6.49 ± 0.84	0.293
Left-colon BBPS, mean ± SD	2.13 ± 0.48	2.13 ± 0.44	2.13 ± 0.44	2.17 ± 0.44	0.587
Transverse-colon BBPS, mean ± SD	2.18 ± 0.50	2.10 ± 0.55	2.19 ± 0.57	2.16 ± 0.49	0.306
Right-colon BBPS, mean ± SD	2.19 ± 0.43	2.14 ± 0.46	2.21 ± 0.46	2.16 ± 0.43	0.238
Adequate BBPS, n/N (%)	244/276 (88.4%)	238/278 (85.6%)	243/281 (86.5%)	251/275 (91.3%)	0.178
Procedural withdrawal time, median [IQR], s	378 [281-518]	354 [243-578]	379 [275-548]	380 [269-596]	0.694
ADR, n/N (%)	93/277 (33.6%)	78/278 (28.1%)	106/281 (37.7%)	78/275 (28.4%)	0.042

Note. The bubble-score and continuous global P values are from Kruskal-Wallis tests; binary outcomes use chi-square tests. One invalid group-A BBPS record was excluded from total, left-colon, and adequacy analyses. ADR, adenoma detection rate; BBPS, Boston Bowel Preparation Scale; IQR, interquartile range.

Table 4. Factorial effects of pre-procedure dose and administration timing

Outcome	Effect	600 mg vs 1,200 mg Estimate (95% CI)	P	1 h vs immediate Estimate (95% CI)	P	Interaction P
Bubble score: odds of a worse category	OR	1.080 (0.858-1.361)	0.512	0.806 (0.640-1.015)	0.067	0.889
Total BBPS	MD	0.079 (-0.024 to 0.182)	0.133	0.077 (-0.026 to 0.180)	0.143	0.452
Adequate BBPS	RR	0.988 (0.946-1.033)	0.606	1.021 (0.978-1.067)	0.343	0.053
Procedural withdrawal time	GMR	0.935 (0.876-1.000)	0.049	1.029 (0.963-1.099)	0.405	0.663
Adenoma detection	aRR	1.253 (1.054-1.490)	0.010	1.068 (0.901-1.266)	0.446	0.677

Note. Effects are from additive factorial models; the interaction P value comes from the corresponding interaction model. Bubble score uses a proportional-odds model. Continuous models use heteroscedasticity-robust standard errors. Withdrawal time was log-transformed. The ADR model was adjusted for age, sex, indication, and family history of gastrointestinal cancer. aRR, adjusted risk ratio; GMR, geometric mean ratio; MD, mean difference; OR, odds ratio; RR, risk ratio.

Table 5. Adjusted modified Poisson model for adenoma detection

Variable	Adjusted risk ratio	95% CI	P value
600 mg vs 1,200 mg before colonoscopy	1.253	1.054-1.490	0.010
1 hour later vs immediately after PEG	1.068	0.901-1.266	0.446
Age, per year	1.011	1.003-1.020	0.006
Male vs female	1.324	1.109-1.580	0.002
Routine health check vs symptom investigation	1.073	0.844-1.366	0.564
Post-polypectomy surveillance vs symptom investigation	1.120	0.841-1.492	0.437
Other tumour screening/monitoring vs symptom investigation	1.185	0.767-1.831	0.444
Inflammatory bowel disease vs symptom investigation	0.520	0.212-1.276	0.153
Other indication vs symptom investigation	1.088	0.507-2.337	0.828
Family history of gastrointestinal cancer	0.494	0.217-1.128	0.094

Note. Modified Poisson regression with robust standard errors; n=1,109 because two age values were missing. The dose-by-timing interaction was not significant (P=0.677) and was omitted from the additive model. PEG, polyethylene glycol.

Figures

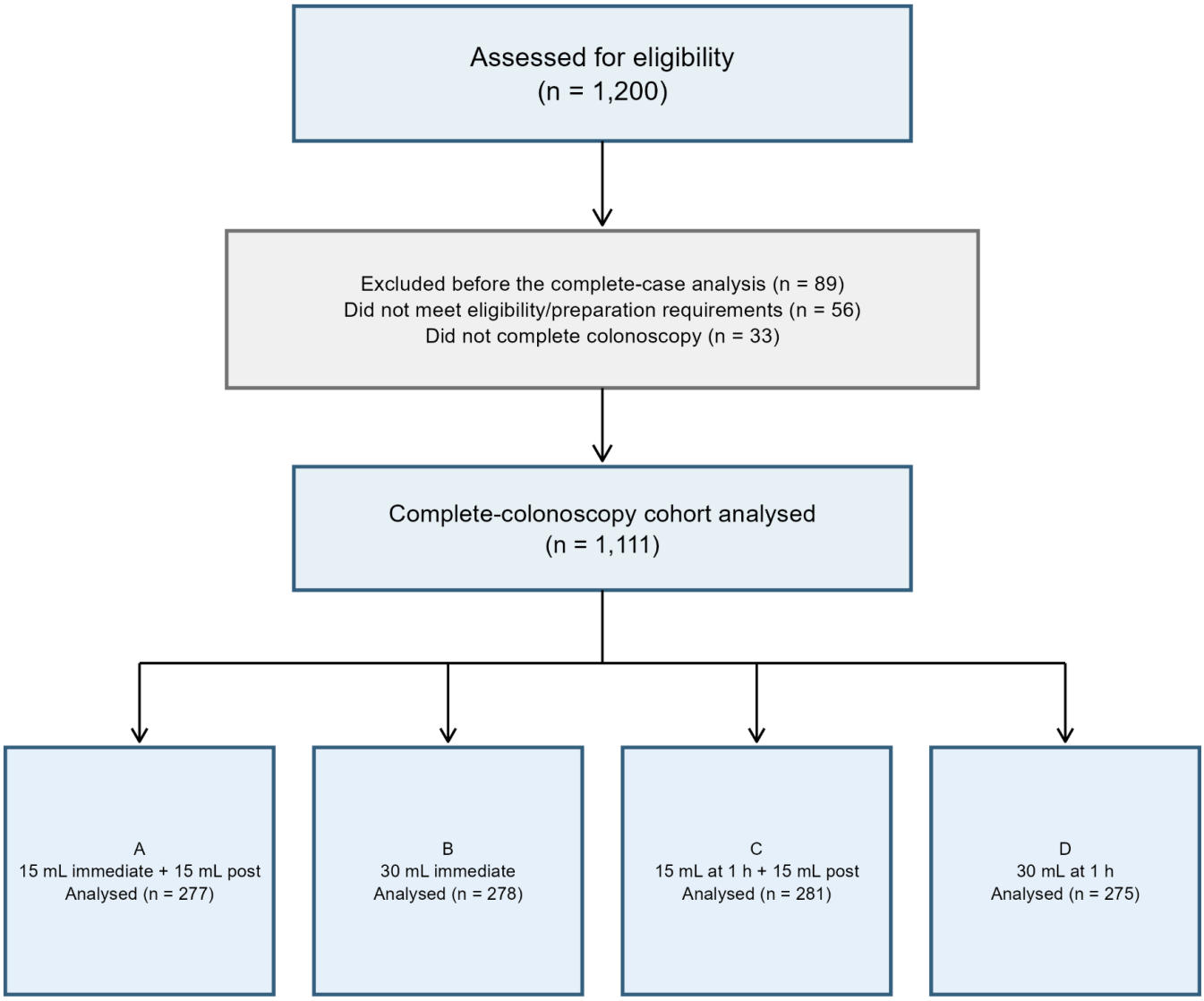

Figure 1

Participant flow based on the available analysis records. Arm-specific counts before the complete-colonoscopy cohort were not available.

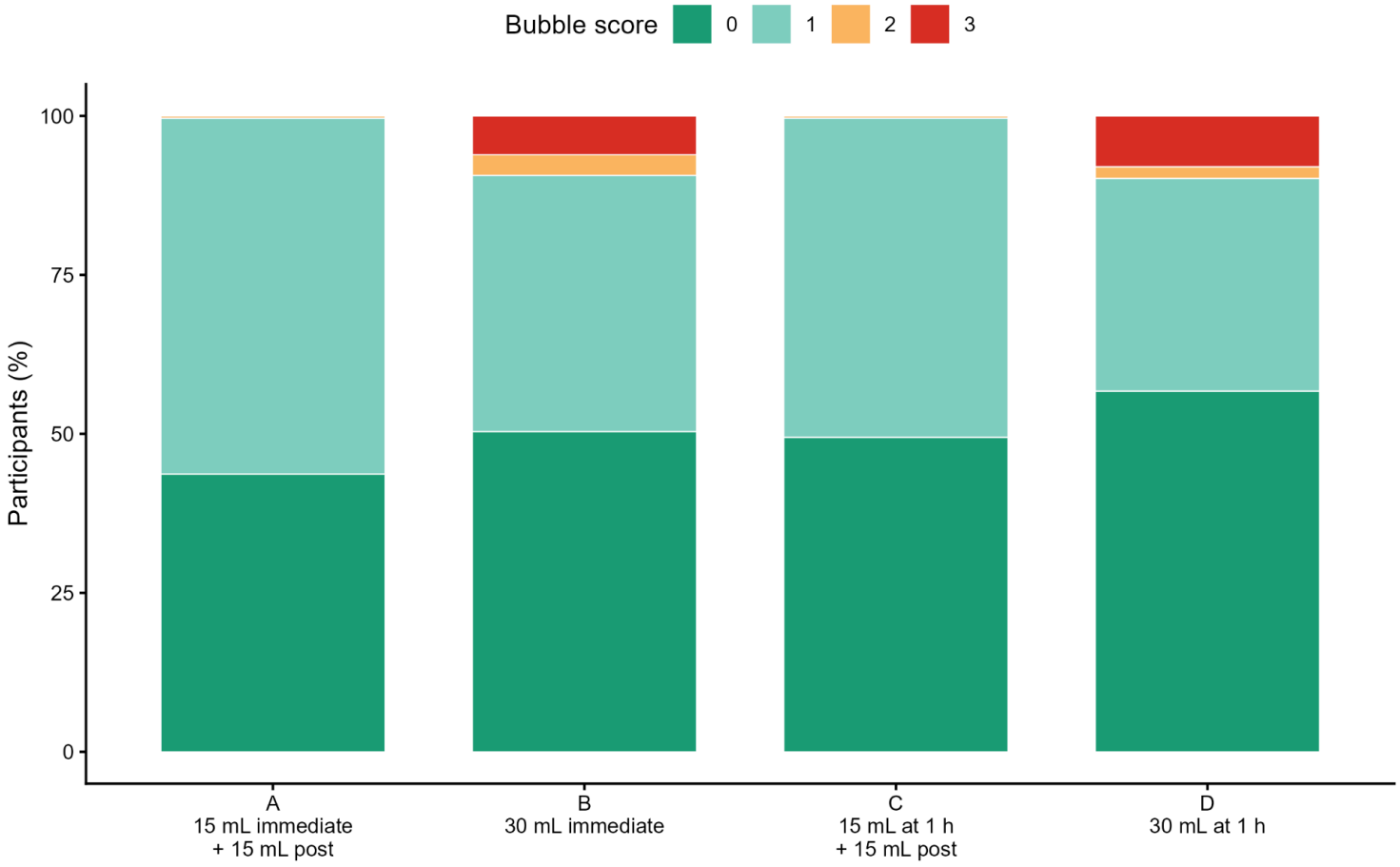

Figure 2

Distribution of the primary bubble score by randomized arm. Bubble-score distributions were comparable across the four groups (P=0.288).

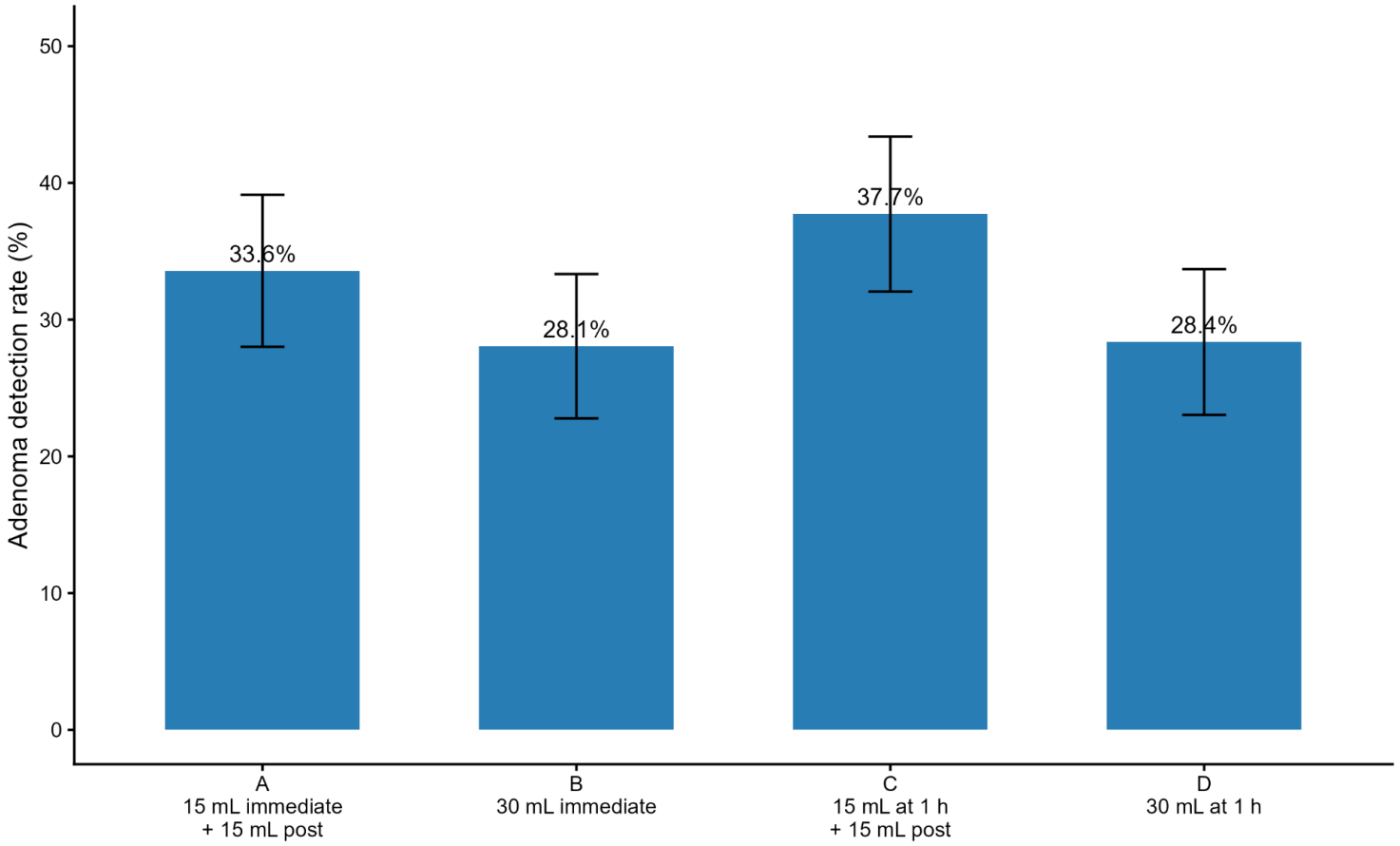

Figure 3

Adenoma detection rate by randomized arm. Error bars are approximate 95% confidence intervals for each proportion.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2025editablechecklist.docx
- TableS1S2.docx