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Cimetropium bromide does not improve polyp and adenoma detection during colonoscope withdrawal

A randomized, double-blind, placebo-controlled study

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Abstract

Background: Endoscopic inspection of colonic mucosa is disturbed by colonic folds and peristalsis, which may result in missed polyps. Cimetropium bromide, an antispasmodic agent, inhibits peristalsis and colonic spasms, which may improve polyp detection. The purpose of this randomized, double-blind, placebo-controlled study was to investigate whether cimetropium bromide could improve polyp and adenoma detection in the colorectum and right colon.

Methods: Patients undergoing screening or diagnostic colonoscopy were randomized to receive intravenous cimetropium bromide (5 mg) or placebo after cecal intubation. The primary outcomes were the number of polyps per patient (PPP) and adenomas per patient (APP); secondary outcomes were the polyp detection rate (PDR), adenoma detection rate (ADR), and advanced neoplasm detection rate (ANDR).

Results: A total of 181 patients were analyzed; 91 patients received cimetropium bromide and 90 patients received placebo. Cimetropium bromide and placebo groups did not significantly differ in the PPP and APP for the colorectum (1.38 ± 1.58 vs 1.69 ± 2.28, $P = .298$; 0.96 ± 1.27 vs 1.11 ± 1.89, $P = .517$, respectively) and right colon (0.70 ± 0.95 vs 0.78 ± 1.21, $P = .645$; 0.47 ± 0.81 vs 0.51 ± 0.81, $P = .757$, respectively). Two groups also did not significantly differ in the PDR, ADR, and ANDR for the colorectum and right colon. Furthermore, there were no difference between groups in the PPP, APP, PDR, ADR, and ADNR in a sub-analysis of expert and non-expert endoscopists.

Conclusions: Cimetropium bromide did not improve polyp and adenoma detection in the colorectum and right colon during colonoscope withdrawal, regardless of the expertness of the endoscopist. However, its use may be helpful in patients with active peristalsis or for beginning endoscopists during standard colonoscopy without a transparent cap.

Abbreviations: ADR = adenoma detection rate, ANDR = advanced neoplasm detection rate, APP = number of adenomas per patient, PDR = polyp detection rate, PPP = number of polyps per patient.

Keywords: adenoma, cimetropium bromide, colonoscopy, polyp

1. Introduction

The detection and removal of adenomatous polyps via colonoscopy is highly effective in the prevention of colorectal cancer, and reduces the incidence and mortality of colorectal cancer.[1–3] However, colonoscopy is not perfect; the rate of missed polyp is still reported as 8% to 37%.[4–7] Missed lesions during colonoscopy are closely related to the presence of blind spots in colonoscopy, which occur more frequently in the right colon due to the high-rise folds and frequent peristalsis. Accordingly, several studies have reported that there are a greater number of missed adenomas in the right colon compared to that in the left colon.[8–10]

Recently, advanced imaging technologies (e.g., high-definition colonoscopy, virtual chromoendoscopy, wide-angle colonoscopy, and full spectrum endoscopy [FUSE]) and new accessories that attach to the tip of the colonoscope (e.g., a transparent cap, Endocuff, and Endoring) have been introduced to improve polyp detection. Furthermore, antispasmodic agents, which are commonly used in gastrointestinal endoscopy to inhibit peristalsis, have been shown to affect adenoma detection by decreasing mucosal movement and allowing better visualization of the

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mucosa.[11] However, hyoscine butylbromide has been reported to not improve polyp detection in numerous studies[12–15] with the exception of 2 studies.[16,17] Cimetropium bromide, a quaternary ammonium compound chemically related to scopolamine, exhibits antispasmodic activity by competing with acetylcholine at the muscarinic receptors in the smooth muscle of gastrointestinal tract.[18] In South Korea, cimetropium bromide has been used to improve the visualization of the mucosa via the inhibition of peristalsis; however, its effect on polyp detection during colonoscopy has not yet been established. Therefore, we evaluated the effect of cimetropium bromide on polyp and adenoma detection during colonoscope withdrawal in a randomized, double-blind, placebo-controlled study.

2. Methods

2.1. Patients and methods

This study was conducted at the Pusan National University Yangsan Hospital (PNUYH) from January 2014 to December 2014. Two hundred outpatients (age, 18–80 years) who underwent colonoscopy for screening (64 patients) or diagnostic (136 patients) purposes for the first time in their life were enrolled. Exclusion criteria were as follows: previous abdominal surgery, previous colonoscopy, inflammatory bowel disease, and conditions with contraindications for the use of cimetropium bromide (e.g., glaucoma, benign prostatic hyperplasia, and heart disease). Nineteen patients with poor bowel preparation were excluded. Informed consent was obtained from all participants. Following recruitment, patients underwent colonoscopy following authorized protocol. Patients were assigned randomly in a 1:1 ratio to receive either cimetropium bromide or placebo at the point during colonoscopy when the cecum was reached. Thus, 181 patients (45.86% male; mean age, 55.57 ± 10.24 years) were finally included; 91 patients received cimetropium bromide and 90 patients received placebo (Fig. 1). The protocol was approved by the Institutional Review Board of PNUYH (IRB No. 05–2013-059).

2.2. Study design

All patients underwent bowel preparation with polyethylene glycol (PEG; 2L on the day before colonoscopy and 2L on the day of colonoscopy) or sodium picosulfate/magnesium citrate (SP/MC; 1 packet on the day before colonoscopy and 2 packets on the day of colonoscopy). All colonoscopies were performed under moderate conscious sedation with intravenous midazolam and pethidine. Heart rate and pulse oximetry were monitored continuously, and the blood pressure, respiration rate, and sedation score were recorded at 5-minute intervals. All patients underwent cap-assisted colonoscopy (CF-H260L, Olympus Optical Co., Tokyo, Japan) with a 4-mm long transparent cap (D-201-14304; Olympus Optical Co.). The colonoscopies were performed by 2 expert (more than 5 years of experience and more than 3000 cases of colonoscopy), and 2 non-expert colonoscopists (less than 1000 cases of colonoscopy).

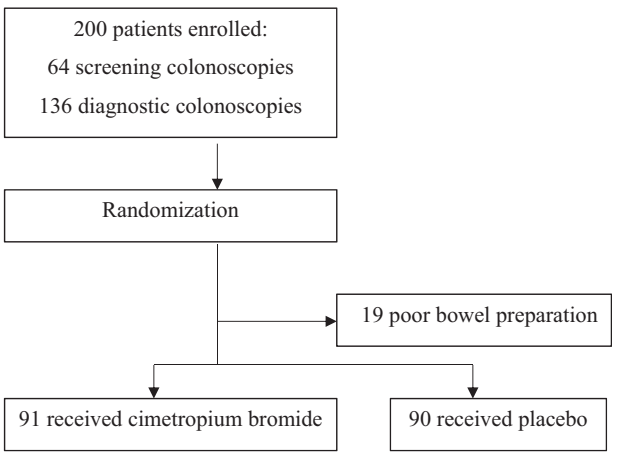

Figure 1. Flow of patients through the study.

Patients were assigned to the cimetropium or placebo group using a random number table. The randomization was performed by the charge nurse, who is an outsider of the endoscope room. The charge nurse measured 1 mL of cimetropium bromide or 1 mL of normal saline on a syringe according to the randomization and delivered it to the endoscopy room. The colonoscopists and patients did not know whether the cimetropium bromide or placebo was given. Colonoscopy was performed after randomization, and patients received either 1 mL (5 mg) cimetropium bromide or 1 mL normal saline intravenously (according to the randomization) when the colonoscope reached the cecum. For quality control, the withdrawal time was maintained at 10 minutes or longer. The withdrawal time included the time for mucosal observation, as well as the time for cleaning, suction, and biopsy. Bowel preparation was evaluated by the endoscopist and graded using the Boston Bowel Preparation scale (BBPS).[19] BPPS scores less than 5 were considered to reflect a poor bowel preparation.[20,21]

2.3. Statistical analysis

The primary outcomes were the number of detected polyps (PPP) and adenomas (APP) per patient. Secondary outcomes were the polyp detection rate (PDR), adenoma detection rate (ADR), and advanced neoplasm detection rate (ANDR). The PDR was defined as the percentage of patients with at least one detected polyp. The ADR was defined as the proportion of patients with at least 1 detected adenoma. The ANDR was defined as the proportion of patients with at least 1 advanced adenoma (an adenoma greater than 1 cm in diameter and/or comprised of least 25% villous features and/or high-grade dysplasia) or cancer.[22] The sample size of this study was determined using data from previous studies with similar background and objectives and 300 patients in each arm were required.

Statistical analyses were performed using PASW for Windows, Version 18.0 (SPSS Inc., Chicago, IL). Quantitative results are expressed as mean ± standard deviation (SD), median, range, or percentage (%). Group differences were evaluated using χ^2 and Fisher exact tests. Separate analyses were conducted for the colorectem and the right colon. In addition, a subanalysis was conducted according to the expertness of the colonoscopist. Multivariate binary logistic regression analyses were performed to determine the factors affecting the ADR and PDR; cimetropium bromide use, sex, age, expertness, diabetic mellitus, hypertension, and BPPS scores (5–6 vs 7–9 points) were included as independent variables. A P value less than .05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 200 patients provided informed consent; however, 19 patients were excluded due to a poor bowel preparation. Thus, a total of 181 patients were analyzed. There were no significant

Table 1

Baseline characteristics of all patients.

	Cimetropium group (N = 91)	Placebo group (N = 90)	P
Gender, male/female	43/48	40/50	.706
Age, mean ± SD, ys	55.45 ± 9.39	55.70 ± 11.09	.870
Diabetes mellitus, n (%)	10 (10.9)	13 (14.4)	.488
Hypertension, n (%)	25 (27.5)	24 (26.7)	.904
Preparation used, n (%)	0.268		
SP/MC	55 (60.4)	47 (52.2)	
4L PEG	36 (39.6)	43 (47.8)	
Indication for colonoscopy, n (%)			.767
Screening	57 (62.6)	57 (63.3)	
Abdominal pain	8 (8.8)	7 (7.8)	
Constipation	5 (5.5)	8 (8.9)	
Loose stool/Diarrhea	9 (9.9)	10 (11.1)	
Positive stool OB	11 (12.1)	6 (6.7)	
Weight loss	1 (1.1)	2 (2.2)	
Bowel preparation (score), n (%)			.336
BBPS 5,6	48 (52.7)	41 (45.6)	
BBPS 7–9	43 (47.3)	49 (54.4)	
Experts/Non-experts, n (%)	20/71 (21.9)	21/69 (23.3)	.828

BPPS = Boston bowel preparation score, OB = occult blood, PEG = polyethylene glycol, SD = standard deviation, SP/MC = sodium picosulfate/magnesium citrate.

differences between the cimetropium bromide and placebo groups in the baseline characteristics, including sample size, age, sex, and bowel preparation (Table 1). Cecal intubation time and withdrawal time also did not differ between the 2 groups. However, the cimetropium bromide group had a significantly higher heart rate at 5 minutes after the injection (90.80 vs 70.24 beats/min, $P < .001$) and at the end of the colonoscopy (87.73 vs. 71.35 beats/min, $P < .001$) compared to that in the placebo group (Table 2).

3.2. PPP, APP, PDR, ADR, and ANDR for the colorectum

The total number of polyps in the colorectum was 126 in the cimetropium group and 152 in the placebo group, while the total number of adenomas was 87 in the cimetropium group and 100 in the placebo group. The cimetropium and placebo groups did not significantly differ in the PPP (1.38 ± 1.58 vs 1.69 ± 2.28, respectively; $P = .298$) and APP for the colorectum (0.96 ± 1.27 vs 1.11 ± 1.89, respectively; $P = .517$) (Table 3). In addition, the cimetropium and placebo groups did not significantly differ in the PDR (62.6% vs 66.7%, respectively; $P = .642$) and ADR for the colorectum (51.6% vs 47.8%, respectively; $P = .657$) (Table 3).

Table 2

Colonoscopic characteristics of cimetropium and placebo groups.

	Cimetropium group (N = 91)	Placebo group (N = 90)	P
Cecal intubation time, median ± IQR, min	5.48 ± 3.43	5.32 ± 3.35	.853
Withdrawal time, median ± IQR, min	16.37 ± 8.16	17.18 ± 8.20	.369
Pulse rates, beats/min			
Baseline	75.52 ± 14.03	75.24 ± 12.48	.891
5 minutes after injection	90.80 ± 15.91	70.24 ± 11.50	< .001
End of colonocopy	87.73 ± 14.37	71.35 ± 11.41	< .001

IQR = interquartile range.

The total number of advanced neoplasia in the colorectum was 2 in the cimetropium group and 7 in the placebo group. All 9 cases of advanced neoplasia were more than ≥1 cm in size, and consisted of 4 adenomas with carcinomas, 2 adenomas with a villous component, and 3 adenomas with high grade dysplasia (HGD) (1 case with a villous component and HGD, and 1 case with HGD and carcinomas). Although the ANDR was higher in the placebo group compared to that in the cimetropium group, the difference was not significant (7.8% vs 2.2%, $P = .100$) (Table 3). In the multivariate binary logistic regression analysis (Table 4), only age was significantly associated with the PDR (odd ratio [OR] 1.045, 95% confidence interval [CI] 1.010–1.081, $P = .010$) and ADR (OR 1.043, 95% CI 1.010–1.078, $P = .011$).

3.3. PPP, APP, PDR, ADR, and ANDR for the right colon

The total number of polyps in the right colon was 64 in the cimetropium group and 70 in the placebo group, while the total number of adenomas was 43 in the cimetropium group and 46 in the placebo group. The cimetropium and placebo groups did not significantly differ in the PPP (0.70 ± 0.95 vs 0.78 ± 1.21, respectively; $P = .645$) and APP for the right colon (0.47 ± 0.81 vs 0.51 ± 0.81, respectively; $P = .757$). In addition, the cimetropium and placebo groups did not significantly differ in the PDR (46.2% vs 47.8%, respectively; $P = .882$), ADR (31.9% vs 34.4%, respectively; $P = .754$), and ANDR for the right colon (0% vs 3.3%, respectively; $P = .121$) (Table 3). In the multivariate binary logistic regression analysis (Table 4), only age was significantly associated with the PDR (OR 1.093, 95% CI 1.052–1.135, $P = .001$) and ADR (OR 1.071, 95% CI 1.031–1.112, $P = .001$).

3.4. PPP, APP, PDR, ADR, and ANDR according to expertness

Among patients treated by a non-expert endoscopist, the cimetropium and placebo groups did not significantly differ in the PPP (1.45 ± 1.69 vs 1.67 ± 2.33, respectively; $P = .056$) and APP (1.06 ± 1.33 vs 1.06 ± 1.98, respectively; $P = .241$) for the colorectum (Table 5). Similarly, among patients treated by an expert endoscopist, the cimetropium and placebo groups did not significantly differ in the PPP (1.15 ± 1.14 vs 1.76 ± 2.17, respectively; $P = .558$) and APP (0.60 ± 1.00 vs 1.29 ± 1.59; $P = .336$) for the colorectum (Table 5). Likewise, the cimetropium and placebo groups did not significantly differ in the PPP and APP for the right colon within expert and non-expert subgroups (Table 5).

Among patients treated by a non-expert endoscopist, the cimetropium and placebo groups did not significantly differ in the PDR, ADR, and ADNR for the colorectum (62.0% vs 68.1%, $P = .482$; 56.3% vs 44.9%, $P = .237$; and 1.4% vs 4.3%, $P = .362$, respectively). Similarly, the groups did not differ in the PDR, ADR, and ANDR for the right colon (46.5% vs 49.3%, $P = .866$; 33.8% vs 34.8%, $P = 1.000$; and 0.0% vs 1.4%, $P = .493$, respectively). Among patients treated by an expert endoscopist, the cimetropium and placebo groups did not significantly differ in the PDR, ADR, and ANDR for the colorectum (65.0% vs 61.9%, $P = 1.000$; 35.0% vs 57.1%, $P = .215$; and 5.0% vs 19.0%, $P = .343$, respectively). Similarly, the groups did not differ in the PDR, ADR, and ANDR for the right colon (45.0% vs 42.9%, $P = 1.000$; 25.0% vs 33.3%, $P = .734$; and 0.0% vs 9.5%, $P = .488$, respectively).

Table 3

PPP, APP, PDR, ADR, and ANDR in colorectum and right colon.

	Colorectum			Right colon		
	Cimetropium group (N = 91)	Placebo group (N = 90)	*P*	Cimetropium group (N = 91)	Placebo group (N = 90)	*P*
Total polyps, n	126	152		64	70	
PPP (mean ± SD)	1.38 ± 1.58	1.69 ± 2.28	.298	0.70 ± 0.95	0.78 ± 1.21	.645
PDR, n (%)	57(62.6)	60 (66.7)	.642	42 (46.2)	43 (47.8)	.882
Total adenomas, n	87	100		43	46	
APP (mean ± SD)	0.96 ± 1.27	1.11 ± 1.89	.517	0.47 ± 0.81	0.51 ± 0.81	.757
ADR, n (%)	47 (51.6)	43 (47.8)	.657	29 (31.9)	31 (34.4)	.754
ANDR, n (%)	2 (2.2)	7 (7.8)	.100	0 (0)	3 (3.3)	.121

ADR = adenoma detection rate, ANDR = advanced neoplasia detection rate, APP = adenomas per patient, PDR = polyp detection rate, PPP = polyps per patient.

Table 4

Multivariate binary logistic regression analysis of PDR and ADR in colorectum and right colon.

	Colorectum				Right colon			
	PDR		ADR		PDR		ADR	
	OR	*P*	OR	*P*	OR	*P*	OR	*P*
Cimetropium	1.198	.575	0.835	.557	1.043	.895	1.096	.784
Sex (M)	0.929	.823	0.699	.251	0.722	.320	0.655	.207
Age	1.045	.010	1.043	.011	1.093	.001	1.071	.001
Experts	1.052	.904	1.230	.604	0.972	.945	1.132	.777
Diabetic mellitus	1.335	.595	1.061	.905	1.134	.808	1.052	.922
Hypertension	0.616	.252	0.874	.727	1.584	.261	1.237	.610
BPPS 7–9	0.889	.737	0.768	.429	0.874	.699	0.887	.741

ADR = adenoma detection rate, BPPS = Boston bowel preparation score, OR = odds ratio, PDR = polyp detection rate.

Table 5

PDR, ADR, and ANDR in non-experts and experts group.

		Colorectum			Right colon		
		Cimetropium group (N = 71/20)	Placebo group (N = 69/21)	*P*	Cimetropium group (N = 71/20)	Placebo group (N = 69/21)	*P*
Non-experts (n = 140)	PPP (mean ± SD)	1.45 ± 1.69	1.67 ± 2.33	.056	0.73 ± 1.00	0.74 ± 1.17	.590
	APP (mean ± SD)	1.06 ± 1.33	1.06 ± 1.98	.241	0.51 ± 0.84	0.46 ± 0.72	.445
	PDR, n (%)	44 (62.0)	47 (68.1)	.482	33 (46.5)	34 (49.3)	.866
	ADR, n (%)	40 (56.3)	31 (44.9)	.237	24 (33.8)	24 (34.8)	1.000
	ANDR, n (%)	1 (1.4)	3 (4.3)	.362	0 (0)	1 (1.4)	.493
Experts (n = 41)	PPP (mean ± SD)	1.15 ± 1.14	1.76 ± 2.17	.558	0.60 ± 0.75	0.90 ± 1.34	.531
	APP (mean ± SD)	0.60 ± 1.00	1.29 ± 1.59	.336	0.35 ± 0.67	0.67 ± 1.24	.750
	PDR, n (%)	13 (65.0)	13 (61.9)	1.000	9 (45.0)	9 (42.9)	1.000
	ADR, n (%)	7 (35.0)	12 (57.1)	.215	5 (25.0)	7 (33.3)	.734
	ANDR, n (%)	1 (5.0)	4 (19.0)	.343	0 (0)	2 (9.5)	.488

ADR = adenoma detection rate, ANDR = advanced neoplasia detection rate, PDR = polyp detection rate, SD = standard deviation.

4. Discussion

The majority of colorectal cancers progress in an adenoma-carcinoma sequence.[23,24] Detecting and removing adenomatous polyps via colonoscopy can reduce the incidence of colorectal cancer and cancer-related deaths.[1–3] However, even with the introduction of advanced imaging technologies and accessories,[25–28] the rates of missed polyps and adenomas in colonoscopy are still high, and the prevention of proximal colon cancer via screening colonoscopy is unclear.[4–7,29] As missed lesions tend to be located at blind spots on colonoscopy, the use of antispasmodic drugs may aid in polyp and adenoma detection. Theoretically, the use of antispasmodic drugs would decrease mucosal movement and allow improved visualization of the mucosa for polyp and adenoma detection, especially in the right colon.[11] Hyoscine N-butylbromide, atropine, glucagon, L-menthol, and cimetropium bromide are well-known antispasmodic drugs. Cimetropium bromide is widely used to inhibit peristalsis and improve visualization during colonoscopy in South Korea.[30] The antispasmodic effect of cimetropium bromide begins promptly (within 1 minute) after injection and has a half-life of 50 minutes.[31] Cimetropium-related side effects include mild tachycardia and dry mouth.[31–33] In the present study, there was significant increase in pulse rate at 5 minutes after injection and at the end of colonoscopy; however, no serious adverse events were observed. Thus, cimetropium bromide use in colonoscopy for polyp and adenoma detection is safe.

Recently, several studies have reported that the use of an antispasmodic as a premedication for colonoscopy does not have a significant effect on the PDR and ADR[12–15] however, 2 studies have shown a significant effect.[16,17] In the present study, cimetropium bromide did not improve polyp and adenoma detection, consistent with the majority of the previous studies. However, many endoscopists empirically feel that antispasmodics are useful for the visualization of the mucosa via the inhibition of spasms and peristalsis; thus, they are widely used. The reasons for the lack of an improvement in polyp detection with antispasmodic use in the present study may be as follows. First, cap-assisted colonoscopy with a 4-mm long transparent cap was performed in all procedures. The cap allows the endoscopist to maintain a continuous visual field around the colonic bends and to inspect thoroughly the blind mucosa by keeping an adequate distance between the tips of the colonoscope and the colonic mucosa and depression of the folds. This effect is in line with that expected from the use of antispasmodics; thus, the use of cap-assisted colonoscopy to improve the visualization of the mucosa may have reduced the difference in polyp and adenoma detection between the cimetropium and placebo groups. Consistent with this hypothesis, the ADRs in the cimetropium and placebo groups in the present study (51.6% and 47.8%) were twice as high as the recommended ADR (25%).[34] Second, the most important factor in polyp detection is the quality of the endoscopist, as appropriate withdrawal techniques and vigilance for polyps can improve the ADR regardless of antispasmodic use.[35] During the most recent monthly quality assessment, the ADR had resulted to be approximately 50% for all endoscopists in the present study, and was high for both non-expert and expert endoscopists, which may also have reduced the difference in polyp and adenoma detection between the cimetropium and placebo groups. In contrast, for beginning endoscopists who cannot perform the appropriate withdrawal techniques, the use of an antispasmodic may help in the detection of polyps by improving the visualization of the mucosa. The non-experts in the present study were not beginners and were capable of appropriate withdrawal techniques. Third, active peristalsis and spasms during colonoscopy did not occur in all patients. Inclusion of patients with inactive peristalsis and no spasms may have diluted the effect of antispasmodic use on polyp detection. A previous study suggested that polyp detection may be improved by spasmolysis in patients with more active colonic spasms.[17]

The present study has several limitations to discuss. First, this is a single-center study with a relatively small number of cases. The present study only included patients who underwent colonoscopy for the first time in their life. Therefore, we did not enroll the actual goal of 300 cases, even though there were 6688 colonoscopies during the study period. Second, we could not analyze group differences in polyp detection according to the shape and size of the polyps. An analysis of small-sized and flat-shaped polyps may reveal a significant difference in polyp detection between the 2 groups. Third, as previously described, cap-assisted colonoscopy may have interfered with the comparison of polyp detection between the 2 groups. Therefore, for a more accurate comparison, studies using colonoscopy without a transparent cap are needed. A fourth limitation is that the relatively short duration of the effect, and individual time-differences in the response to cimetropium bromide, may not have allowed a proper spasmolysis for polyp detection during colonoscope withdrawal. Therefore, further studies with an objective analysis of spasmolysis are needed.

In conclusion, the present randomized, double-blind, placebo-controlled study demonstrated no benefit of cimetropium bromide use on polyp and adenoma detection during colonoscope withdrawal. Although there are no serious adverse events and the cost is low, the routine use of cimetropium bromide is not necessary. However, its use may be helpful in patients with active peristalsis or for beginning endoscopists who have not developed the appropriate withdrawal techniques during standard colonoscopy without a transparent cap. Further studies are required to confirm the effect of cimetropium bromide on polyp detection in these situations.

Author contributions

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