Mechanisms of hyoscine butylbromide to improve adenoma detection: A case-control study of surface visualization at simulated colonoscope withdrawal

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Background and study aims: Antispasmodics may improve mucosal visualization during colonoscope withdrawal, potentially improving polyp and adenoma detection. Meta-analysis and case-control studies suggest a 9% to 13% relative increase in adenoma and polyp detection. We aimed to assess the impact of hyoscine butylbromide on the expected visualization during colonoscope withdrawal using a CT colonography (CTC) simulation.

Patients and methods: Datasets from a previous CTC study examining the effect of antispasmodic were re-analyzed with customised CTC software, adjusted to simulate a standard colonoscopic view. Eighty-six patients received intravenous (IV) hyoscine butylbromide 20 mg, 40 mg or no antispasmodic. Main outcome measurements at unidirectional flythrough, simulating colonoscope withdrawal, were percentage colonic surface visualization, numbers and sizes of unseen areas, and colonic length.

Results: Use of antispasmodic was associated with a significant relative increase in percentage surface visualization of 2.6% to 3.9%, compared with no antispasmodic, $P<0.006$. Total numbers of missed areas and intermediate sized (300–1000 mm^2) missed areas were significantly decreased, by approximately 20%. There were no differences between the 20-mg and 40-mg doses. Mean colonic length (161–169 cm) was unchanged by antispasmodic.

Conclusions: IV hyoscine butylbromide at simulated colonoscope withdrawal was associated with significant increases in surface visualization, which might explain up to half the improvement in adenoma detection seen in clinical studies.

Introduction

In recent years, emphasis has been placed on colonoscopic quality, leading to reinvestigation of basic elements of colonoscopic extubation technique, such as withdrawal time, changing patient position, operator technique, and bowel preparation [1–4], that have been shown to impact polyp and adenoma detection rates. Basic technique can be improved to maximize adenoma detection with minimal additional financial cost.

Routine use of antispasmodics during colonoscopy is controversial. Although the literature is inconsistent, in some studies, hyoscine butylbromide has been shown to accelerate colonoscopic intubation, and it may reduce patient procedural discomfort [5–7]. Other antispasmodics that have been investigated include glucagon, dicyclomine, hyoscyamine, atropine, peppermint oil, and warm water [8–14]. None of these has been shown to reduce intubation time, and only topical peppermint oil and warm water have been shown to reduce spasm scores or pain [9,14]. Until recently, very little investigation has been done of use of antispasmodics during the extubation or withdrawal phase of colonoscopy; however, the rationale for use of antispasmodics during extubation is not unreasonable. By reducing smooth muscle tone, haustral folds can be flattened, allowing better visualization of blind spots behind them, and peristaltic waves may be reduced, giving a still colonic surface on which to detect lesions. Indeed, studies using unblinding at CT colonography (CTC) suggest that most polyps missed by optical colonoscopy are on the back of folds in these blind spots [15]. A recent meta-analysis reported a relative risk for adenoma detection of 1.09 (95% confidence interval 0.91–1.31) and for polyps of 1.13 (95% CI 0.92–1.38), numerically but non-significantly, in favor of hyoscine [16], and in a very large cohort study (n=31088), the proportion of patients with at least one adenoma detected was 50.1% with hyoscine versus 44.5% without (relative increase 12.6%, $P<0.001$) with

similar improvements for advanced adenoma detection rates [17]. This pair of estimates suggests that the relative improvement in adenoma detection rate is likely to be on the order of 9% to 3%.

Despite the theoretical advantages of routine use of antispasmodics and expert recommendation, implementation has been variable worldwide. In a United Kingdom national colonoscopy audit, for example, only 20% of colonoscopists used antispasmodics routinely [18]. In the United States and France, hyoscine butylbromide is unlicensed for colonoscopy. Furthermore, use of antispasmodics is not recommended in the US multi-society taskforce guidelines on quality in colonoscopic technique [19]; however, the converse is true in Japan, where usage is routine.

Hyoscine butylbromide is the antispasmodic most commonly used during colonoscopy. Data from the CTC and barium enema literature suggest that it is superior to both glucagon and placebo in improving colonic distension and diagnostic quality [20–22]. Assessing the effect of hyoscine butylbromide on mucosal visualization during colonoscopic extubation is technically very challenging. However, recently developed, customized CTC software is able to calculate the amount of colonic surface seen during simulated colonoscope withdrawal, corrected for the field of view of a modern colonoscope, as we have previously reported [23].

The purpose of our study was to approximate the changes in percentage surface visualization, numbers and sizes of missed areas, and changes in colonic length that are likely to be encountered with intravenous (IV) hyoscine butylbromide when colonoscopy is simulated by CTC in patients suspected of having colorectal cancer. Given that this is a simulation of colonoscopic withdrawal, the study results should be viewed cautiously; however, they may give some insight into the mechanism by which hyoscine appears to improve adenoma detection in clinical studies.

Patients and methods

The protocol for the original CTC study was approved by our Local Regional Ethics Committee and all patients gave written informed consent. Specific permission for this additional analysis was sought from and granted by the same Ethics Committee.

CTC dataset selection and spasmolytic administration

CTC datasets were collated from a previous randomized trial assessing the effect of hyoscine butylbromide on colonic distension at CTC in 136 patients. All patients were clinically suspected of having colorectal cancer. The methods used in the previous CTC study have been reported in detail elsewhere and are described briefly below. [21]

The first 20 patients received 20 mg hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Bracknell, England) IV given just before colonic gas insufflation (see below). Thereafter patients were randomised to receive either no antispasmodic or a slow bolus of 20 mg (given as before) or 40 mg of hyoscine butylbromide. If patients were randomised to 40 mg, 20 mg was given before the colonic gas insufflation in the prone position (performed first) and then an additional 20 mg was given before the supine scan (performed immediately after the prone scan). Therefore, only supine datasets reflect the full 40-mg dosage for those randomised to 40 mg. Contraindications to antispasmodic were recently symptomatic ischemic heart disease and a history of closed-angle glaucoma. Three patients originally randomized to the antispasmodic group had contraindications and were assigned to the no antispasmodic group. Minimization was used to balance the groups as accrual progressed. In total, 40 patients received no antispasmodic, 66 received 20 mg, and 30 received 40 mg hyoscine butylbromide. Due to data loss, data corruption, or inadvertent destruction, only 86 of the original 136 datasets were available for the current study, 33 without antispasmodic, 35 assigned to 20 mg, and 18 assigned to 40-mg hyoscine butylbromide.

CTC protocol

All patients underwent colonic insufflation of carbon dioxide via manual compression of a previously filled enema bag, until approximately 2500 mL had been introduced or to the limit of patient tolerance. Gas was introduced via either a thin rectal tube or a rectal balloon catheter, with allocation via a separate randomization sequence. Patients were scanned initially in the prone position. After this, those who were allocated to 40 mg hyoscine had further administration as described above. All patients then had additional gas introduced via the rectal catheter to account for carbon dioxide absorption during the prone scan. Scout scans were used before data acquisition in each position to determine if distension was adequate.

CTC dataset analysis

The 86 datasets were analysed with customized proprietary CTC software (V3 D colon; Viatronix, Stonybook, NY) by a gastroenterologist who had received formal training in CTC examination (over 40 endoscopically validated datasets) and had experience with the software functionality. The technique has been described previously [23]. In brief, the software automatically segments gas-filled colon from surrounding organs and calculates a centerline within the segmented lumen from the anal verge to the cecum, facilitating automated 3-dimensional (3 D) endoluminal navigation (**Fig. 1 a**). The user is able to check the segmentation via a 3 D colon map and adjust if necessary. The software tracks the amount of colonic surface within the field of view during automated endoluminal navigation and calculates the amount of visualized colonic surface area (expressed as a percentage of the whole colonic surface), and the number, size, and distance from the anal verge of all missed areas (i. e., areas of unseen colonic surface) [24]. The visualized surface is "painted" green by the software, thus indicating missed areas to the observer (**Fig. 1 b**). Total colonic length is also reported automatically, calculated via the centreline.

Customization of the software for the purposes of the current study allowed the observer to vary the field of view of the endoluminal "camera" from 0 to 180 degrees, and to download missed area data onto a computer spreadsheet.

The observer then performed an automated flythrough without detours along the software-determined centerline, with the virtual camera facing the cecum, equivalent to the view during optical colonoscope withdrawal. The field of view was set to 140 degrees for the current study, specifically to simulate a standard, optical colonoscope. The observer performed the flythrough on both prone and supine series from all 86 CTC datasets, recording percentage mucosal visualization, number of missed areas [total, intermediate sized (300 – 1000 mm^2), and large (> 1000 mm^2)], and total colonic length.

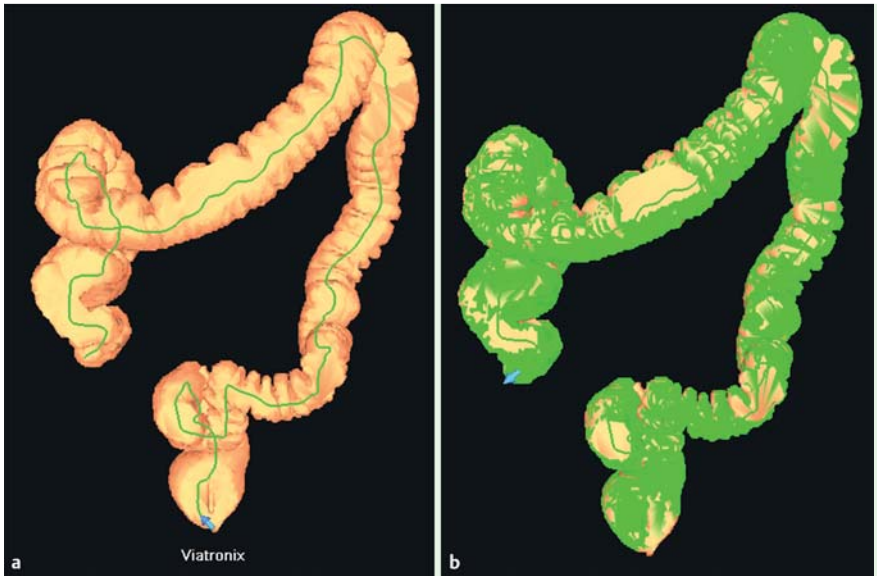

Fig. 1 **a** Overview of the colon with centerline for navigation (green) automatically drawn by the CT colonography software. **b** Overview after unidirectional 3D-endoluminal flythrough facing the cecum, where the software had "painted" visualized areas green. Unseen areas remain beige.

Statistical analysis

The primary outcome measure was the percentage surface visualization achieved in patients receiving either no antispasmodic or antispasmodic. The supine position was chosen for analysis because it was felt to give the best distension overall, particularly in the transverse colon, and of the two available options (supine or prone), was felt to best model usual patient position during colonoscopy. Age, percentage colonic surface visualization, missed areas, and colonic length were compared between the two groups using unpaired, 2-tailed, t-tests. Sex ratios and use of a rectal balloon catheter were compared with Fisher's exact test. Further data analyses were performed for a split by dose of antispasmodic. Probability values were considered significant at the 5% level and P values ≥ 0.05 but < 0.1 were considered to indicate a statistical trend.

Results

Datasets (n = 86) were initially split into those who had received antispasmodic (either 20 mg or 40 mg, n = 53) and those who had not (n = 33) (**Table 1**). There were no significant differences in age, sex ratio, or use of rectal balloon catheter between the two groups. When antispasmodic was used, there was a highly significant relative increase in the total colonic surface visualized (2.6 and 3.9% for prone and supine datasets, respectively), equivalent to relative reductions in percentage surface unseen of 18% and 25% (**Table 1**).

The total number of missed areas of any size was reduced significantly by antispasmodic, from approximately 90 missed areas to just over 65 (28% relative reduction). When the missed areas were subclassified by size, there was a significant reduction in intermediate-size (300 – 1000 mm^2) missed areas in the supine position, and a trend toward reduction in the prone position, from approximately 25 to 20 (20% relative reduction) missed areas. There were no significant differences in the numbers of large (> 1000 mm^2) missed areas (**Table 1**).

No significant difference in total colonic length was seen with antispasmodic, with an overall length of between 160 and 170 cm. Colonic lengths ranged from 110 to 247 cm, with 6 (11%) and 3 (6%) colons being longer than 200 cm in the prone and supine positions, respectively, in the antispasmodic group versus 3 (9%) and 2 (6%), respectively, in the group that received no antispasmodics (**Table 1**).

The supine dataset was then divided into three groups: Those who received no antispasmodic (n = 33), those who received 20 mg (n = 35), and those who received 40 mg (n = 18) (**Table 2**). Again significant increases were seen in total colonic visualization for both 20 mg and 40 mg compared with no antispasmodic, with effect sizes similar to those seen in the antispasmodic versus no antispasmodic analysis. There was, however, no significant difference for any of the parameters tested when the 20-mg and 40-mg groups were compared. Similarly there were significant reductions or there was a trend toward significance for reduction in total missed areas and intermediate (300 – 1000 mm^2) sized missed areas between the no-antispasmodic group and both the 20-mg and 40-mg groups, but not between the 20-mg and 40-mg groups (**Table 2**). There were no significant differences in the numbers of large (> 1000 mm^2) missed areas or in colonic length among any of the groups.

Discussion

Principal findings

This study suggests that use of hyoscine butylbromide increases the relative percentage of colonic surface visualized at simulated colonoscope withdrawal by approximately 4%. There were also significant relative decreases of approximately 20% in both the total number of missed areas and the intermediate-sized (300 – 1000 mm^2) missed areas with the use of antispasmodic. A reduction in intermediate-sized missed areas may be important clinically because these areas might harbor a small (6 – 9 mm) or diminutive (≤ 5 mm) polyp.There was little difference between prone and supine positioning; however, supine data are preferred to represent the best simulation of optical colonoscopy as the best distension is achieved, because the transverse colon can be collapsed in the prone position at CT colonography [23]. Furthermore, prone positioning is rarely used during the withdrawal phase of colonoscopy [2].

Colorectal length was not significantly altered by antispasmodic. Total colonic length was 169 cm when prone and 161 cm in

	Position	Hyoscine butylbromide IV		*P* value
		No (n = 33)	Yes (n = 53)[1]	
Age, years		65.8 ± 11.0 (41 – 89)	62.2 ± 12.4 (34 – 85)	0.16
Sex, male/ female (%)		13 (39 %)	28 (53 %)	0.27[2]
Balloon catheter (%)		17 (52 %)	29 (55 %)	0.83[2]
% colonic surface visualization	Prone	87.3 ± 3.9 (77 – 95)	89.6 ± 3.6 (78 – 95)	0.005
	Supine	86.4 ± 4.3 (75 – 95)	89.8 ± 3.3 (78 – 96)	< 0.001
Total number missed areas	Prone	87.9 ± 30.7 (25 – 157)	65.6 ± 26.3 (22 – 178)	0.002
	Supine	89.0 ± 34.8 (28 – 156)	68.6 ± 27.7 (22 – 159)	0.011
Missed areas 300 – 1000 mm^2	Prone	24.6 ± 10.2 (6 – 55)	20.2 ± 10.8 (6 – 75)	0.091
	Supine	25.5 ± 12.5 (8 – 54)	19.6 ± 10.1 (7 – 62)	0.044
Missed areas > 1000 mm^2	Prone	6.8 ± 4.8 (1 – 20)	7.0 ± 5.1 (2 – 33)	0.64
	Supine	7.2 ± 5.9 (1 – 28)	6.6 ± 4.3 (0 – 23)	0.73
Total colonic length, cm	Prone	168.8 ± 20.3 (133.4 – 222.0)	166.9 ± 28.0 (115.0 – 246.7)	0.73
	Supine	161.3 ± 25.2 (109.9 – 231.2)	161.3 ± 26.3 (106.7 – 212.4)	1.00

Data presented as mean ± standard deviation (range).
[1] 20 mg or 40 mg hyoscine
[2] Fisher's exact test

Table 1 Surface visualization, missed areas, and colonic length with antispasmodic versus no antispasmodic.

Table 2 Results for varying doses of antispasmodic, supine position.

Variable	Hyoscine Butylbromide IV			*P* value		
	Nil[1] (n = 31)	20 mg[1] (n = 34)	40 mg[1] (n = 14)	Nil vs 20 mg	Nil vs 40 mg	20 vs 40 mg
Age, years	65.5 ± 10.3 (41 – 81)	61.7 ± 13.1 (34 – 85)	64.2 ± 9.8 (45 – 83)	0.20	0.68	0.48
Sex, male (%)	12 (39 %)	15 (44 %)	9 (64 %)	0.80[2]	0.34[2]	0.20[2]
Balloon catheter (%)	16 (52 %)	18 (53 %)	7 (50 %)	1.0[2]	1.0[2]	1.0[2]
% Colonic surface visualization	86.4 ± 4.3 (75 – 95)	89.6 ± 3.6 (78 – 95)	90.4 ± 2.6 (84 – 95)	0.002	< 0.001	0.43
Total number missed areas	89.0 ± 34.8 (28 – 156)	68.7 ± 29.3 (22 – 159)	72.5 ± 24.3 (40 – 114)	0.011	0.081	0.40
Missed areas 300 – 1000 mm^2	25.5 ± 12.5 (8 – 54)	20.0 ± 11.5 (8 – 62)	18.8 ± 6.3 (7 – 26)	0.071	0.023	0.97
Missed areas > 1000 mm^2	7.2 ± 5.9 (1 – 28)	6.2 ± 4.3 (1 – 23)	7.7 ± 4.4 0 – 16	0.45	0.76	0.35
Total colonic length, cm	161.3 ± 25.2 (109.9 – 231.2)	158.3 ± 28.3 (106.7 – 212.4)	164.9 ± 18.3 (135.1 – 193.0)	0.66	0.59	0.35

Data presented as mean ± standard deviation (range).
[1] Supine scans unavailable for all patients leading to a reduced number of datasets for analysis
[2] Fisher's exact test

supine scans. The proportion of patients with colons longer than 200 cm – between 6 % and 11 % – is roughly half the reported proportion of patients who have "difficult" colonoscopies, and may reflect potential looping problems rather than fixation or diverticulosis [25].

Comparing 20-mg to 40-mg IV hyoscine, there were no significant differences, suggesting that the lower dose is adequate to optimize visualization and decrease missed areas. Interestingly, the proportion of missed areas overall that occurred in the rectum and sigmoid (20 % – 22 %) was much less than might have been predicted from the proportion of the colonic length examined (37 % – 39 %), suggesting that missed areas are more common in the proximal colon, an area already known to be at higher risk for cancer misses and failed cancer prevention after colonoscopy [26, 27].

Comparison with other studies

The benefit of hyoscine butylbromide in improving adenoma and polyp detection have been reviewed in a recent meta-analysis, which reported a relative risk for adenoma detection of 1.09 (95 % confidence interval 0.91 – 1.31) and polyps 1.13 (95 % CI 0.92 – 1.38) numerically but nonsignificantly in favor of hyo-

scine [16], and in a very large cohort study (n = 31088) from the National Health Service bowel cancer screening program, the proportion of patients with at least one adenoma detected was 50.1% with hyoscine versus 44.5% without (relative increase 12.6%, $P < 0.001$) with similar improvements for advanced adenoma detection rates 27.4% vs 31.8%, $P < 0.001$. These differences persisted after correction for other variables. Therefore, the 4% increase in surface visualization seen in our study in the supine position, most representative of optical colonoscopy, might explain up to half the benefit for polyp detection seen in clinical studies in which a 9% to 13% relative increase is reported. The residual benefit may be due to having a still surface for polyp detection

Mean colonic length reported here, 161 to 169 cm, is broadly similar to that seen in other studies assessing length with CTC, but is longer than the length reported in studies that used barium enema to assess colonic length, 145 – 155 cm [20, 25, 28].

One study has investigated the potentially adverse effects of hyoscine on hemodynamics at colonoscopy by giving larger doses (40 mg) to accentuate responses [6]. The relevance of these findings seems limited if such a large dose is unlikely to be needed clinically for optimal visualization, as suggested in the current study.

Study limitations

This study has a number of limitations. The original participants, whose data were analyzed further here, were recruited prospectively from outpatient clinics and had symptoms suggestive of colorectal cancer. Unfortunately only two-thirds of the dataset was available for review, making the current study less representative of the original population and possibly adding unknown bias, although data loss was random and groups remain well matched. As discussed above, the simulation represents a "straight pull-back" withdrawal technique where the colonoscopist attempts to keep the tip of the scope in the center of the lumen and withdraws slowly. In reality, colonoscopists use a more active withdrawal technique, which may increase the amount of colonic surface seen beyond that reported here. The data presented, therefore, should not be regarded as reflecting absolute percentage visualization at optical colonoscopy, but rather, a guide to likely effect sizes if spasmolysis were employed. We assumed that increased surface visualization leads to increased polyp detection, which is logical but unproven; however, recent data from a clinical trial that used a retrograde viewing auxiliary imaging device to improve surface visualization showed an overall increase in adenoma detection of 11.0%, very similar to the predicted increase of 12.1% in surface visualization in a previous simulation of such a device using the current CTC simulation [23, 29]. Although the simulation gives a quantitative measurement of effect size in terms of surface visualization and sizes of missed areas, antispasmodic has other effects. In particular, it reduces peristalsis, which immobilizes the surface visualized, and could potentially be as or more important than improvements in surface visualization.

Clinical implications

The current study would support the clinical use of hyoscine butylbromide to optimize colonoscopic visualization, but suggests that the effect size is modest; however, that may explain up to half the benefit reported for adenoma detection seen in clinical studies. The minimal cost involved (one 20-mg ampoule Buscopan® for injection, £0.29, British National Formulary, 2015) for this modest benefit may be acceptable.

Overall the lack of change in colonic length seen in this study would argue against those who have concerns regarding antispasmodics increasing colonic length at colonoscopy. Excessive colonic length estimated by barium enema is known to predict difficult colonoscopy [30].

From our study data, it seems unlikely that there is likely to be further benefit from doses of hyoscine beyond 20 mg. We were not able to assess whether even smaller doses might give the same clinical benefit.

Conclusions

In this anatomical simulation study of colonoscope withdrawal to examine the mechanism of benefit on adenoma detection, we found that IV administration of hyoscine butylbromide increased the percentage of colonic surface visualization by approximately 4%, with a relative decrease of 20% in the number of clinically significant (300 – 1000 mm^2) missed areas. This mechanism may explain up to half the improvement in adenoma and polyp detection seen in clinical studies.

Competing interests: Drs. Halligan and Taylor are NIHR senior investigators. No author has a conflict of interest related to this study

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