

Impact of Hyoscine Bromide Use on Polyp Detection Rate During Colonoscopy: A Systematic Review and Meta-Analysis

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of death worldwide. Polyp detection rate (PDR) and adenoma detection rate (ADR) are key focus in endoscopic research for CRC screening and prevention. Use of anti-spasmodic agents during colonoscopy to help identify adenomas and polyps has remained a controversial topic. Hyoscine butyl bromide (HBB) is the most commonly used anti-spasmodic agent in patients undergoing colonoscopy. Some randomized controlled trials (RCTs) have questioned the clinical efficacy and safety of routine use of HBB for polyp and adenoma detection rates.

Methods: We conducted a systematic search in PubMed and MEDLINE from inception until February 10, 2018, for studies which compared HBB with placebo. We used RevMan version 5.3 for analysis. Procedural end-points were polyps, adenomas, and advanced adenoma detection rates, mean number of polyps detected and cecal intubation time.

Results: We included seven RCTs with 2,588 patients in our analysis. A total of 1,301 patients were randomized to HBB arm and 1,287 to the placebo arm. There was no significant difference in the primary outcome of polyp detection rate, 654 in HBB group vs. 616 in the placebo group, (odds ratio (OR) = 1.11, confidence interval (CI) = 0.93 - 1.34, P = 0.25). There was no difference in secondary outcomes of adenoma detection rate, 430 in HBB group vs. 396 in the placebo group, (OR = 1.06, CI = 0.89 - 1.26, P = 0.51), advanced adenoma detection rate, 92 in HBB vs. 95 in placebo group (OR = 0.95, CI = 0.70 - 1.30, P = 0.76), mean number of polyps detected (point estimate = 0.12, CI = 0.00 - 0.23, P = 0.05), adenomatous polyps (OR = 0.84, CI = 0.39 - 1.81, P = 0.65) and cecal intubation time (point estimate =

0.73, CI = -1.98 - 0.52, P = 0.25) between the two groups.

Conclusions: The use of HBB in patients undergoing colonoscopy does not appear to improve polyp or adenoma detection rates. It showed a non-significant trend of increased mean number of polyps detected with HBB.

Keywords: Colonoscopy; Hyoscine butyl bromide; Colorectal polyps; Colorectal adenomas; Advanced adenomas; Adenoma detection rate; Polyp detection rate

Introduction

Colorectal cancer (CRC) is one of leading cause of death due to cancers worldwide. Colonoscopy is the gold standard procedure for the diagnosis and treatment of several colonic disorders including benign and malignant neoplasms. Adenoma detection rate (ADR) is a key quality component and a well-recognized strategy in CRC secondary prevention. The incidence of CRC is declining due to early screening and removal of adenomas [1].

Polyp detection rate (PDR) and ADR have been the focus of endoscopic research and are widely used to measure the quality of colonoscopy [2]. Studies have shown that polyps or adenomas may remain undetected or missed [3]. Antispasmodic agents have a long history of use in colonoscopy for a variety of indications. The pathophysiology behind administering these agents is that it can increase the visualization of the colonic surface by reducing spasms and flattening haustral folds [4].

HBB is the most commonly used anti-spasmodic agent in patients undergoing colonoscopy. Multiple RCTs have been conducted using HBB and have shown variable results regarding PDR and ADR. In our meta-analysis, we have analyzed the results of all the RCTs available to date using HBB and their impact on PDR to provide a better understanding of the topic.

Methods

Search strategy

The systematic review and meta-analysis are conducted in accordance with the Preferred Reporting Items for Systematic

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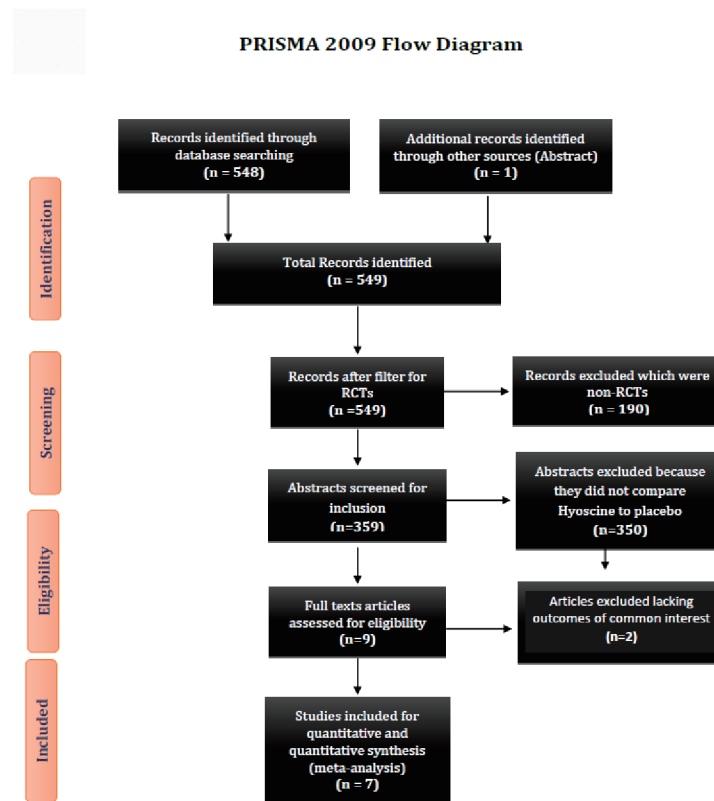


Figure 1. Showing the PRISMA 2009 study flow diagram. PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized control trial.

Reviews and Meta-analyses (PRISMA) guidelines [5].

Data sources

A planned literature search of MEDLINE and PubMed databases was conducted from inception to February 10, 2018 using Medical Subject Headings (MeSH) and keyword terms. Search terms used were combined with the Boolean operator “AND” and “OR.” We used following search strategy for selecting studies (hyoscine butylbromide) OR (buscopan) OR (scopolamine) AND (adenoma) OR (polyp) AND (colonoscopy).

Study selection protocol

We selected RCTs in which patients were allocated to receive HBB or placebo at the time of cecal intubation. We used studies fulfilling the following inclusion criteria for analysis: 1) Prospective study design; 2) Adult patients > 18 years of age; 3) Written in English; 4) PDR or ADR as an outcome for the study. Those studies which failed to meet these inclusion criteria were excluded.

A total of 548 articles were initially identified, using the MeSH term and keywords. We found one abstract from the literature search. We excluded 190 articles with the filter for RCTs. Totally, 359 trials were identified and reviewed in detail.

There were 350 studies which were excluded as they either did not compare hyoscine to placebo or were not randomized. Two studies lack endpoint of interests. Seven prospective RCTs were included for final comparison and statistical analysis (PRISMA diagram) (Fig. 1). Baseline characteristics and salient features of each study are summarized in Tables 1 and 2 [6-12].

Outcomes for analysis

The primary outcome measure was the PDR, defined as the proportion of patients in whom at least one polyp was detected. Secondary outcomes included: 1) The ADR, defined as the proportion of patients in whom at least one adenoma was detected; 2) The advanced ADR (AADR), defined as the proportion of patients in whom at least one advanced adenoma (i.e., adenoma 1 cm and/or adenoma with advanced histologic features, such as a villous component and/or high-grade dysplasia) was detected; 3) Mean number of polyps detected; 4) Cecal intubation time; 5) Polyp located proximal to the splenic flexure; 6) Polyp located distal to the splenic flexure; 7) Adenomatous polyps.

Risk of bias and assessment of study quality

Two authors (M.Y.K., and A.D) independently examined the titles and abstracts of all the articles to exclude irrelevant stud-

Table 1. Baseline Characteristics of Patients

Studies	Corte et al [6]	Santos et al [7]	Lee et al [8]	Brouwer et al [11]	Ristikankare et al [9]	Byun et al [12]	Rondonotti et al [10]
Journal	Endoscopy	Clinics	Hepato-Gastroenterology	Gastrointestinal Endoscopy	Scandinavian Journal of Gastroenterology	Gastrointestinal Endoscopy	Digestive and Liver Disease
Design	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT
Population	Hyoscine Placebo	Hyoscine Placebo	Hyoscine Placebo	Hyoscine Placebo	Hyoscine Placebo	Hyoscine Placebo	Hyoscine Placebo
Sample size	303	298	58	340	75	103	202
Age	60.6 ± 11.2	61.4 ± 10.4	59.4 ± 8.5	61.5	61.6 ± 8.2	59.8 ± 8.9	57.3 ± 11.5
		≥ 50 (166 pts), < 50 (54 pts)	≥ 50 (173 pts), < 50 (47 pts)				57.3 ± 11.5
Male no (%)	162 (53.5)	157 (52.7)	27 (46.6)	(45.9)	37	30	90 (44.5)
BMI (kg/m ²)	NR	NR	NR	NR	26.5 ± 4.5	26.1 ± 4.1	NR
Active smoking	NR	NR	22.4%	NR	15%	21%	NR
Prior surgery*	40 (13.4)	40 (13.2)	NR	NR	46	61	NR
Diverticulosis ^a	25 (8.3)	19 (6.4)	NR	(31.7)	NR	NR	NR
Prior colonoscopy ^b	26 (8.6)	23 (7.7)	NR	NR	(39%)	(36%)	NR
Indication							
CRC screening	81 (26.7)	86 (28.9)	NR	NR	NR	NR	47 (23.2)
Polyps surveillance	58 (19.1)	52 (17.4)	NR	31 (9.1)	(11)	(11)	51 (25.3)
Standard indication	168 (55.4)	164 (55)	NR	NR	NR	NR	NR
Anemia	NR	NR	NR	20 (5.9)	(21)	(39)	79 (39.1)
Rectal bleeding	NR	NR	NR	60 (17.6)	(19.2)	NR	81 (40.5)
Abdominal pain	NR	NR	NR	55 (16.2)	(23)	(11)	NR
Unexplained diarrhea/ABH	NR	NR	NR	31 (9.1)	(10.2)	(27)	NR
Screening after resection of CRC	NR	NR	NR	13 (3.8)	(4.8)	NR	NR
Family history of CRC	NR	NR	NR	23 (6.8)	(7.2)	NR	NR
IBD dysplasia screening	NR	NR	NR	4 (1.2)	(2.1)	NR	NR
Other indication	NR	NR	NR	NR	(24)	(13)	NR

*Prior abdominal or pelvic surgery. ^aDiverticulosis present or >10. ^bPrior colonoscopy or prior difficult colonoscopy. CRC: colorectal cancer; ABH: altered bowel habits; IBD: irritable bowel disease; NR: not reported; pts: patients.

Table 2. Characteristics of Randomized Controlled Trials

Study	Corte et al [6]	Santos et al [7]	Lee et al [8]	Brouwer et al [11]	Ristikankare et al [9]	Byun et al [12]	Rondonotti et al [10]
Design	Prospective randomized double-blind placebo-controlled trial	Prospective randomized placebo-controlled trial	Prospective randomized double-blind controlled trial	A prospective, double-blind, placebo-controlled, randomized, clinical trial.	Prospective double-blind, randomized, placebo-controlled, clinical trial	Prospective randomized, double-blinded, placebo-controlled trial	Prospective randomized, double-blind, placebo-controlled trial
Country	Australia	Brazil	Korea	Netherlands	Finland	NR	Italy
Publication year	2012	2017	2010	2012	2015	2009	2013
Journal	Endoscopy	Clinics	Hepato-Gastroenterology	Gastrointestinal Endoscopy	Scandinavian Journal of Gastroenterology	Gastrointestinal Endoscopy	Digestive and Liver Disease
Enrollment	March 2009 to March 2011	March to July 2015	January to June 2008	January 21 to June 21, 2011	March 2012 to March 2014	July 2008 to September 2008	NR
Population	Patients over 40 years old who were scheduled for routine outpatient colonoscopy	CRC screening, surveillance or a clinical suspicion of CRC	Patients between the age 50 and 70 years and had no potential risk factors for CRC	Outpatients aged 30 years or older referred and accepted for colonoscopy	Outpatients scheduled for diagnostic colonoscopy between ages 45 and 75 years	NR	Adult outpatients (18 - 80 years of age) referred for colonoscopy
Intervention vs. comparison	Hyoscine vs. placebo	Hyoscine vs. placebo	Hyoscine vs. placebo	Hyoscine vs. placebo	Hyoscine vs. placebo	Hyoscine vs. placebo	Hyoscine vs. placebo

ies. Selected articles’s full texts were individually assessed for eligibility based on the above-mentioned inclusion criteria. The Cochrane Collaboration’s Risk of Bias tool was used to determine bias in the randomized trials meeting eligibility criteria [13].

Data synthesis and analysis

Statistical method

We performed statistical analysis using statistical software Rev-Man Version 5.3 Copenhagen. We used random effects model and Mantel-Haenszel method for the statistical analysis of dichotomous data to calculate the odds ratio, and we used inverse variance for the continuous data to estimate the mean difference. We also expressed our results using the forest plots. We considered two-sided P-value of < 0.05 as statistically significant.

We used seven RCTs for our analysis. We summarized baseline characteristics in Table 1 and characteristics of individual RCT in Table 2. We utilized Cochrane collaboration’s tool risk assessment of bias in randomized trials for the quality assessment of RCTs, Table 3 [6-12].

Heterogeneity

We used I² and Chi² statistics to calculate the heterogeneity. Inter-study variability (variability between studies) compared to intra-study variability (variability within studies) was estimated with the I² statistic. I² > 50% explains substantial heterogeneity as described in the Cochrane Handbook for Systematic Reviews for Interventions, Version 5.1.0, Part 2: General Methods for Cochrane Reviews [14]. We performed sensitivity analysis for substantial heterogeneity.

Results

Qualitative analysis

We included seven RCTs with 2,588 patients in our analysis. A total of 1,301 patients were randomized to hyoscine arm and 1,287 to the placebo arm.

The primary endpoint was polyp detection rate. The secondary endpoints were: 1) Adenoma detection rate; 2) Advanced lesion detection rate; 3) Mean number of polyps detected; 4) Cecal intubation time; 5) Polyp location proximal to the splenic flexure; 6) Polyp location distal to the splenic flexure; and 7) Adenomatous polyps.

Primary endpoint

Polyp detection rate

PDR was also similar between the two arms, with 654 in HBB group compared to 616 in the placebo group (odds ratio (OR)

Table 3. Cochrane Risk of Bias

Name	Random sequence	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Reporting bias
Byun et al [12]	Not reported	Not reported	Blinded	Not reported	No	Not reported
	Unclear	Unclear	Low risk	Unclear	Low Risk	Unclear
Lee et al [8]	Central randomization with computer generated codes	Not reported	Blinded (complete)	Not reported	No	Not reported
	Low risk	Unclear	Low risk	Unclear	Low Risk	Unclear
Corte et al [6]	Central randomization with computerized algorithm	No	Single arm blinded*	Not reported	No	Not reported
	Low risk	High risk	Low risk	Unclear	Low risk	Unclear
Brouwer et al [11]	Not reported	Not reported	Not reported	Yes	No	Not reported
	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Rondonotti et al [10]	Central randomization using computer generated list	Randomization list	Single arm blinded*	Not reported	No	Not reported
	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Ristnikankre et al [9]	Block randomization using sealed envelopes	Sealed and coded envelopes	Blinded (complete)	Not reported	No	Not reported
	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Santos et al [7]	Web generated	Sealed envelopes	Blinded	Yes	No	Not reported
	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear

*Administering nurse not blinded.

= 1.11, confidence interval (CI) = 0.93 - 1.34, P = 0.25, I² = 20% (Fig. 2).

430 in the HBB group vs. 396 in the placebo group (OR = 1.06, CI = 0.89 - 1.26, P = 0.51, I² = 0%) (Fig. 3a).

Secondary endpoints

Advanced lesion detection rate

Adenoma detection rate

There was no difference in the detection rate of advanced lesions, between the two arms, HBB arm had 92 vs. placebo arm had 95 (OR = 0.95, CI = 0.70 - 1.30, P = 0.76, I² = 0%) (Fig. 3b).

There was no difference in the ADR between the two groups,

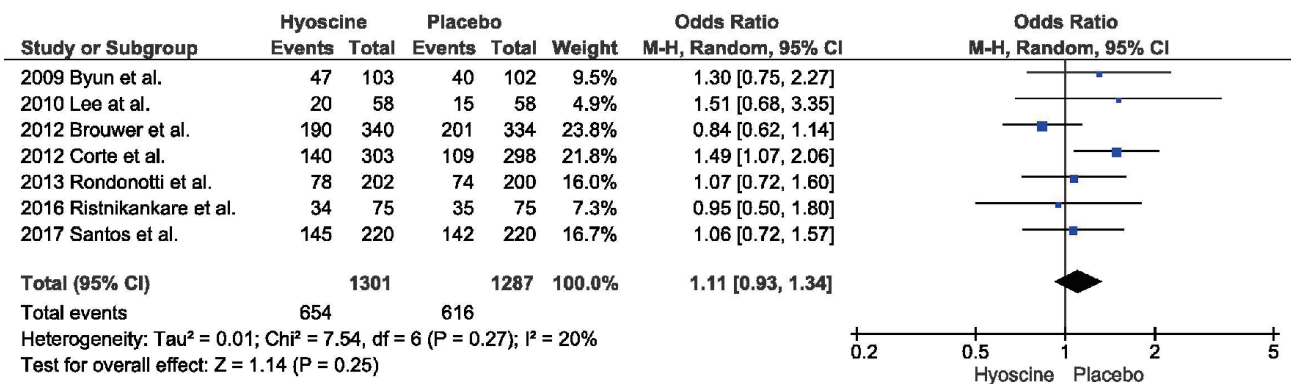


Figure 2. Primary outcome: polyp detection rate.

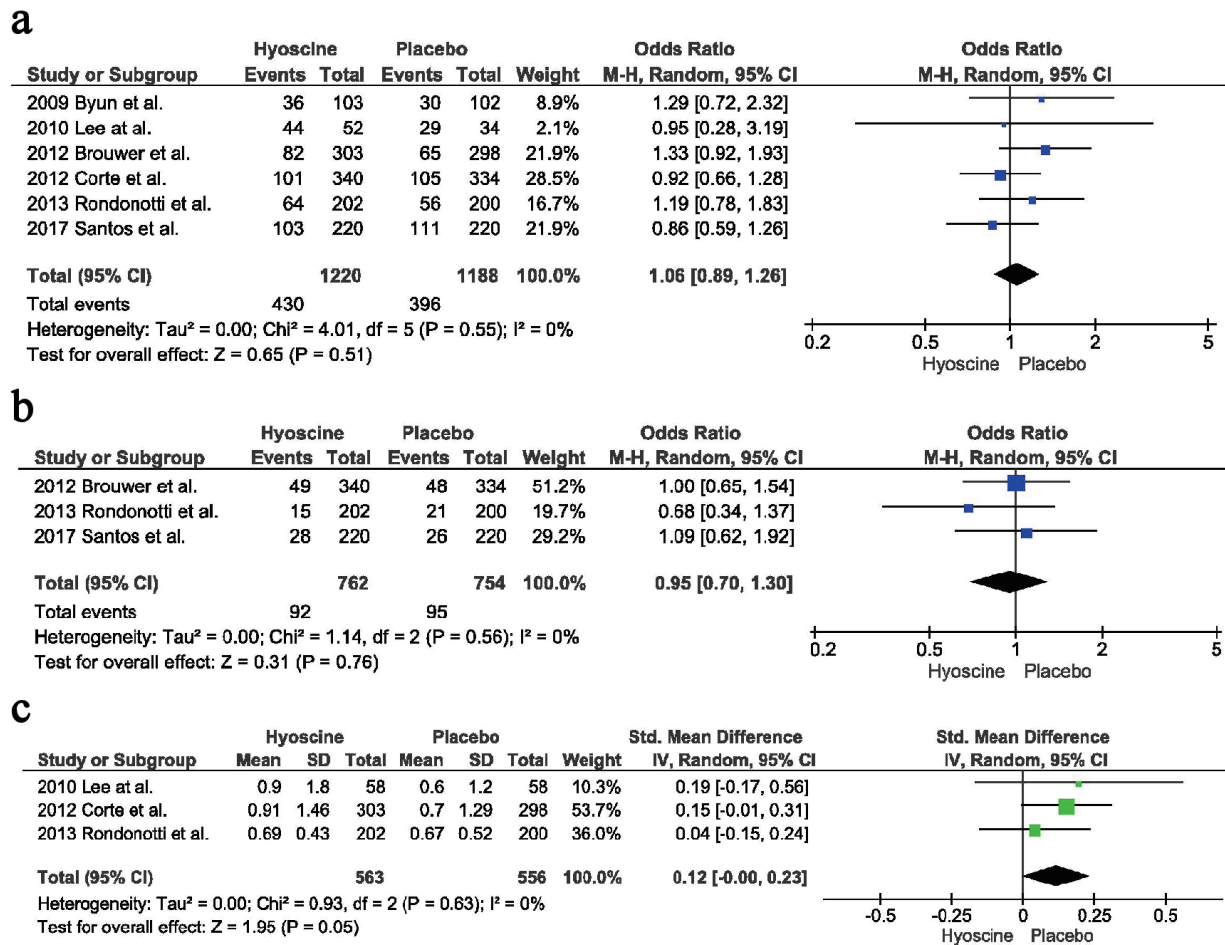


Figure 3. Secondary outcomes: (a) Adenoma detection rate. (b) Advance adenoma detection rate. (c) Mean number of polyps detected.

Mean number of polyps detected

There was no difference in the mean number of polyps detected between the two arms, 563 in the HBB group vs. 556 in the placebo group with a point estimate of 0.12, CI = -0.00 - 0.23, P = 0.05, I² = 0%) (Fig. 3c).

Cecal intubation time

Two studies reported the cecal intubation time. There was no difference between the two groups, with point estimate of -0.73, CI = -1.98 - 0.52, P = 0.25, I² = 97%. On running the sensitivity analysis without Ristikankare et al heterogeneity reduced to 0% with a trend towards decreased incubation time in the HBB arm compared to the placebo arm (Fig. 4a).

Polyp location proximal to the splenic flexure

There was no difference in the identification of polyps located

proximal to splenic flexure, 198 in the HBB arm vs. 209 in the placebo arm, OR = 0.89, CI = 0.59 - 1.35, P = 0.58, I² = 52%. Only two studies reported the location of polyps proximal to the splenic flexure; therefore we could not perform the sensitivity analysis (Fig. 4b).

Polyp location distal to the splenic flexure

Similarly there was no difference in the identification of polyps located distal to the splenic flexure, 224 in the HBB arm vs. 206 in the placebo arm, OR = 1.19, CI = 0.86 - 1.63, P = 0.29, I² = 24% (Fig. 4c).

Adenomatous polyps

There was no difference in the number of adenomatous polyps identified between the two groups, 295 in the HBB group vs. 298 in the placebo group, OR = 0.84, CI = 0.39 - 1.81, P = 0.65, I² = 78%. Only two studies reported this outcome; there-

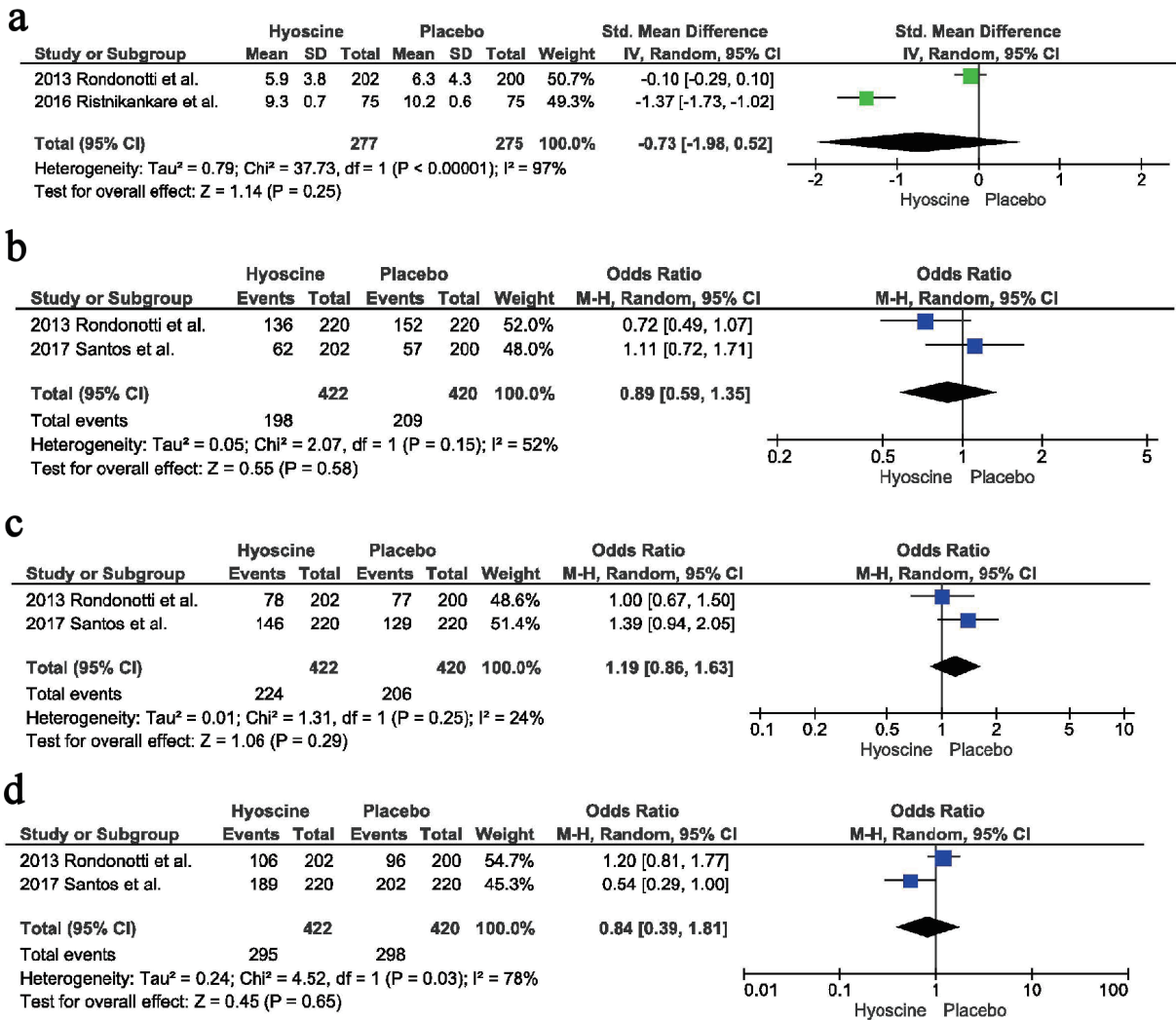


Figure 4. Secondary outcomes: (a) Cecal intubation time. (b) Polyp location proximal to splenic flexure. (c) Polyp location distal to splenic flexure. (d) Adenomatous polyps.

fore sensitivity analysis couldn't be performed (Fig. 4d).

Discussion

Data from several studies showed that colonoscopy could miss up to 22% of adenomas irrespective of their size [3]. Careful mucosal exploration of gut is a key factor in detection of polyps [4], and multiple strategies have been developed to improve the PDR such as use of chromoendoscopy [15], water immersion technique [16, 17] and Third Eye Retroscope [18]. Most colonoscopists use the withdrawal time to examine the colon for detecting polyps during colonoscopy. Strategies that involve visualizing mucosa around the flexures, proximal sides of folds and ileocecal valves have shown to yield higher polyp detection rates [15, 17].

Colonoscopy can be a challenge for the operator due to differences in anatomic mobility and folded structure of the

intestinal mucosa [19]. Air insufflation used during the procedure can lead to intestinal wall or colonic mesentery distension causing discomfort for the patients. Moreover, mobile portions of the colon can lead to loop formation of colonoscope causing further unease to the patients [20, 21].

The benefit of colonoscopy in reducing incidence and mortality of CRC is more significant for distal than for proximal CRC [22, 23]. Non-polypoid lesions are more common on the right side of the colon and failure of colonoscopy to diagnose such lesions could partially explain the development of interval more aggressive neoplasms [24]. Failure to diagnose these lesions could be attributed to inadequate bowel preparation [25, 26], colonoscopy technique, colonoscope withdrawal time [27], and polyp location [28, 29].

Since the advent of colonoscopy, antispasmodics have been tried adjunctively in the certainty that the resultant reduction in colonic spasm would improve outcomes. Antispasmodic agents have a long history of use in colonoscopy for

a variety of indications. Commonly used antispasmodics in colonoscopy were HBB, glucagon and peppermint oil. HBB is the well-studied anti-spasmodic due to its low cost and acceptable safety profile. Radiologists commonly use HBB also for CT colonography and barium enema to facilitate mucosal exploration and decrease colonic motility [30, 31].

There has been controversial data regarding the use of anti-spasmodic agents during colonoscopy to help improve PDR. Studies that have used atropine and glucagon as antispasmodic agents did not show benefit regarding intubation and total procedure time during colonoscopic procedures [32-34]. Initial data demonstrating the efficacy of antispasmodic came from two studies that showed the intravenous use of HBB led to significant decrease in total intubation time and degree of patient discomfort by reducing colon spasms [35, 36]. Two other large observational and retrospective studies reported improved polyp and adenoma detection in patients receiving HBB at the time of cecal intubation compared to placebo [37, 38]. HBB has been shown to facilitate ileal intubation in studies done by Ansari et al and Misra et al [39, 40]. Some studies have shown HBB use before the procedure can lead to adverse effect on colonoscopy procedure time and patient discomfort. The postulated reason is that the decrease colonic muscle tone can make it difficult for the operator to reach the cecum [6, 41].

To explain the disparity in the results seen in the previous studies following aspects should be taken into consideration. These include smaller patient population studied, use of sedative medications, the dose and routes of anti-spasmodic agents used and timing of administration of anti-spasmodic agents. Even though antispasmodic drugs are cheap and safe, their anticholinergic properties have raised cardiovascular safety concerns [35].

We included seven RCTs with 2,588 patients in our analysis. A total of 1,301 patients were randomized to HBB arm and 1,287 to the placebo arm. The primary outcome variable was polyp detection rate. All the included studies for our meta-analysis were well-suited and homogeneous regarding design, reported outcomes, modality, dosage and timing of drug administration, and methods for blinding or masking. By pooled data, we found no differences between the two groups regarding the polyp detection rates, adenoma detection rates, and advanced lesion detection rates. We found no significant difference regarding polyp location proximal or distal to the splenic flexure and mean number of polyps detected. Among the two studies that reported the cecal intubation time, there was no difference between the two arms. Results from our meta-analysis question the use and efficacy of hyosamine during the colonoscopic procedures to improve PDR, ADR or AADR. On the contrary Madhoun et al in their meta-analysis pointed out marginal benefit regarding PDR and ADR in patients who received HBB during colonoscopy [41].

However, HBB seems to increase ADR and PDR in a subset of the population reported in earlier studies. Corte et al demonstrated higher polyp rate in HBB group when administered after cecal intubation as compared to placebo group [6]. Santos et al in their recently published RCT found a higher rate of non-polypoid lesions in the HBB group as compared to placebo group [7]. Lee et al showed that in a selected subgroup

of patients with intense colonic spasms using non validated spasm score > 3 HBB group had more significant ADR compared to placebo group [8]. However, all these RCTs revealed no statistical difference regarding ADR, PDR or advanced ADR in the hyosamine group compared to placebo.

Our paper has several limitations. One of the RCT did not use sedation during the procedure. They also gave HBB before the procedure and at time of cecal intubation [9]. Rest of the RCTs included in the analysis had patients on sedation during the colonoscopy, and HBB was given at the time of cecal intubation. Both these factors could have influenced the PDR or ADR by altering the degree of colonic spasms. The second limitation was that only two RCTs reported cecal intubation time [9, 10] and polyp location [7, 10] which makes it difficult to generalize the results of these two outcomes. The third limitation was that Ristikankare et al reported their mean number of polyps without standard deviation [9]. Therefore we could not use their outcomes in our analysis. Another limitation of the study includes that pathology was not reviewed.

Conclusions

Our meta-analysis showed HBB used during a colonoscopy does not improve PDR or ADR. It showed a non-significant trend of increased mean number of polyps detected with HBB. However few studies have shown the potential benefit of HBB when administered to a subgroup of the population such as with marked colonic spasms. Further RCTs are required focusing on this population to determine any real benefit of HBB in improving ADR or PDR.

Conflict of Interest

There was no conflict of interest to report.

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