

## Hyoscine for polyp detection during colonoscopy: A meta-analysis and systematic review

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### Abstract

**AIM:** To assess the role of hyoscine for polyp detection during colonoscopy.

**METHODS:** Studies (randomized controlled trials or RCTs) that compared the use of hyoscine vs no hyoscine or placebo for polyp detection during colonoscopy were included in our analysis. A search on multiple databases was performed in September 2013 with search terms being "hyoscine and colonoscopy", "hyoscine and polyp", "hyoscine and adenoma", "antispasmodic and colonoscopy", "antispasmodic and adenoma", and "antispasmodic and polyp". Jadad scoring was used to assess the quality of studies. The efficacy of hyoscine was analyzed using Mantel-Haenszel model for polyp and adenoma detection with odds ratio (OR). The  $I^2$

measure of inconsistency was used to assess heterogeneity ( $P < 0.05$  or  $I^2 > 50\%$ ). Statistical analysis was performed by RevMan 5.1. Funnel plots was used to assess publication bias.

**RESULTS:** The search of the electronic databases identified 283 articles. Of these articles, eight published RCTs performed at various locations in Europe, Asia, and Australia were included in our meta-analysis, seven published as manuscripts and one published as an abstract ( $n = 2307$ ). All the studies included patients with a hyoscine and a no hyoscine/placebo group and were of adequate quality (Jadad score  $\geq 2$ ). Eight RCTs assessed the polyp detection rate (PDR) ( $n = 2307$ ). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for PDR (OR = 1.06; 95%CI: 0.89-1.25;  $P = 0.51$ ). Five RCTs assessed the adenoma detection rate (ADR) ( $n = 2015$ ). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for ADR (OR = 1.12; 95%CI: 0.92-1.37;  $P = 0.25$ ). Furthermore, the timing of hyoscine administration (given at cecal intubation or pre-procedure) demonstrated no differences in PDR compared to no hyoscine or placebo. Publication bias or heterogeneity was not observed for any of the outcomes.

**CONCLUSION:** Hyoscine use in patients undergoing colonoscopy does not appear to significantly increase the detection of polyps or adenomas.

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**Key words:** Hyoscine; Antispasmodic; Polyp detection; Colonoscopy

**Core tip:** Hyoscine is used in clinical practice to decrease spasms in the colon during colonoscopy in an effort to improve polyp or adenoma detection. However, this study shows that hyoscine given before the procedure or at time of cecal intubation does not improve polyp or adenoma detection.

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## INTRODUCTION

Colorectal cancer (CRC) is a common and devastating condition with higher incidence in developed countries/western world<sup>[1-4]</sup>. Screening programs have reduced the mortality related to CRC<sup>[5-7]</sup>. Most of these cancers arise from adenomatous polyps which can later progress into dysplasia and cancer; referred to as the adenoma-carcinoma sequence<sup>[8]</sup>. Colonoscopy is an important screening tool and has a large part in the reduction of CRC occurrence by removing these adenomatous polyps<sup>[9]</sup>.

Adenoma detection rate (ADR) and polyp detection rate (PDR) are pivotal indicators for a quality colonoscopy and inversely related to the development of interval carcinoma<sup>[10,11]</sup>. Many polyps are missed with colonoscopy because of various factors, such as bowel preparation quality<sup>[12,13]</sup>, polyp position<sup>[14,15]</sup>, and colonic spasm<sup>[16,17]</sup>. Different antispasmodic agents including glucagon<sup>[18]</sup>, dicyclomine<sup>[19]</sup>, and atropine<sup>[20]</sup> have shown no significant benefit to facilitate colonoscopy.

Hyoscine butylbromide is a relatively safe antispasmodic anticholinergic agent which is commercially available in many forms (sublingual, injectable, and pills) and is frequently used to treat patients with functional bowel pain<sup>[21]</sup>. It blunts the response of colonic neurons to muscarinic and nicotinic stimulation which leads to inhibition of smooth muscle contraction in the colon<sup>[22]</sup>. It is associated with significantly less anticholinergic side effects due to not crossing the blood-brain barrier, making it a useful antispasmodic agent<sup>[23]</sup>.

The use of hyoscine as premedication or at the time of cecal intubation during colonoscopy has shown conflicting results for detection of polyps<sup>[17,24-30]</sup>. Therefore, through study of randomized controlled trials (RCTs), hyoscine was compared to no hyoscine or placebo for polyp or adenoma detection during colonoscopy.

## MATERIALS AND METHODS

### Study selection

RCTs comparing hyoscine to no hyoscine or placebo on adults for polyp detection during colonoscopy were included. Criteria for exclusion was pediatric patients, non-randomized controlled trials, and abstract publications from other than the American College of Gastroenterology (ACG) and Digestive Disease Week (DDW) meetings or prior to 2003.

### Data collection and extraction

Data was collected in multiple stages. First, a comprehen-

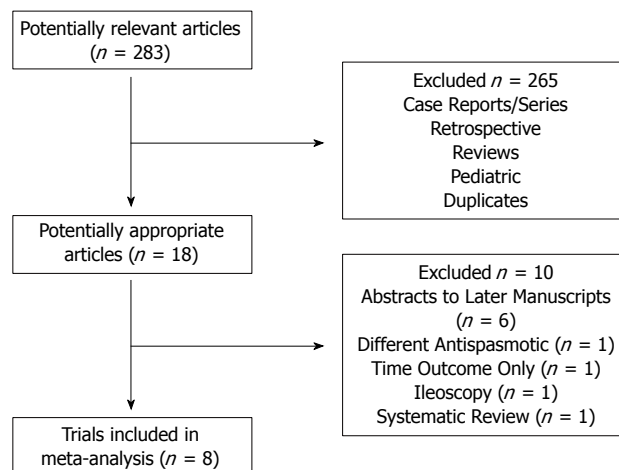


Figure 1 Selection of studies for inclusion in the meta-analysis.

sive search of PubMed/Medline, Embase, Cochrane databases, and CINAHL in September 2013 was conducted. Second, each selected article's references were searched. Lastly, abstracts of DDW and ACG national meetings were searched from 2003-2013. The keywords used for the search included "hyoscine and colonoscopy", "hyoscine and polyp", "hyoscine and adenoma", "antispasmodic and colonoscopy", "antispasmodic and adenoma", and "antispasmodic and polyp". Standard forms were utilized for data extraction by three authors (IA, SA, and MLB) independently with any disagreements ruled on by a fourth author (AC) or mutual agreement. If data was incomplete or unclear, authors were contacted. Study quality was assessed by a Jadad score<sup>[31,32]</sup>. Jadad score ranges from 0 (poor quality) to 5 (excellent quality)<sup>[31]</sup>. It evaluates multiple study parameters related to randomization, blinding, and withdrawals. One point is deducted for each inappropriate criterion<sup>[31]</sup>.

### Statistical analysis

Pooled estimates of PDR and ADR were calculated for the effect of hyoscine or no hyoscine or placebo by odds ratio (OR) with Mantel-Haenszel (fixed effect) model given no heterogeneity identified.

Furthermore, a subgroup analysis was performed in similar fashion for the timing of the hyoscine administration, pre-procedure or during colonoscopy upon cecal intubation.  $I^2$  measure of inconsistency was used to assess heterogeneity (significant if  $P < 0.05$  or  $I^2 > 50\%$ ). Statistics performed by RevMan 5.1 (Review Manager Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Funnel plots, Egger's regression intercept and Begg-Mazumdar rank correlation methods assessed publication bias.

## RESULTS

Search of the electronic databases identified 283 articles (Figure 1). Of these articles, 8 published randomized controlled trials (RCTs) performed at various locations in Europe, Asia, and Australia were included in our meta-

**Table 1** Characteristics of studies included in meta-analysis

Ref.	Study type	Blinding	Location	No. of patients	Hyoscine dose	Hyoscine route	Timing of administration
de Brouwer <i>et al</i> <sup>[26]</sup> 2012	RCT	Double	Netherlands	674	20 mg	IV	Cecal intubation
Byun <i>et al</i> <sup>[24]</sup> 2009	RCT	Double	NR	205	20 mg	IV	Cecal intubation
Lee <i>et al</i> <sup>[17]</sup> 2010	RCT	Double	NR	116	20 mg	IV	Cecal intubation
Kim <i>et al</i> <sup>[27]</sup> 2010	RCT	Double	South Korea	133	20 mg	IM	Premedication
Rondonotti <i>et al</i> <sup>[29]</sup> 2013	RCT	Double	Italy	402	20 mg	IV	Cecal intubation
Mui <i>et al</i> <sup>[28]</sup> 2004	RCT	Yes	China	120	40 mg	IV	Premedication
Saunders <i>et al</i> <sup>[30]</sup> 1996	RCT	Yes	England	56	20 mg	IV	Premedication
Corte <i>et al</i> <sup>[25]</sup> 2012	RCT	Yes	Australia	601	20 mg	IV	Cecal intubation

RCT: Randomized controlled trial; NR: Not reported.

**Table 2** Quality assessment of the studies included in this meta-analysis using Jadad scale

Ref.	Study design	Method of randomization	Double-blind	Method of double-blinding	Description of withdrawals	Total score <sup>2</sup>
de Brouwer <i>et al</i> <sup>[26]</sup> 2012	1	1	1	0	1	4
Byun <i>et al</i> <sup>[24]</sup> 2009 <sup>1</sup>	1	0	1	0	1	3
Lee <i>et al</i> <sup>[17]</sup> 2010	1	1	1	0	1	4
Kim <i>et al</i> <sup>[27]</sup> 2010	1	0	1	0	1	3
Rondonotti <i>et al</i> <sup>[29]</sup> 2013	1	1	1	1	1	5
Mui <i>et al</i> <sup>[28]</sup> 2004	1	1	1	1	1	5
Saunders <i>et al</i> <sup>[30]</sup> 1996	1	1	1	1	1	5
Corte <i>et al</i> <sup>[25]</sup> 2012	1	1	1	1	1	5

<sup>1</sup>Abstract; <sup>2</sup>Jadad Score: 1-5, 5 is excellent and 1 is poor.

analysis, seven published as manuscripts<sup>[17,25-30]</sup> and one published as an abstract<sup>[24]</sup> (Table 1). All included patients with a hyoscine and a no hyoscine/placebo group and were of acceptable quality ( $\geq 2$  on the Jadad scale) (Table 2).

### Polyp detection rate

Eight RCTs assessed the polyp detection rate (PDR) ( $n = 2307$ ). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for PDR (502/1165, 43.1% *vs* 478/1142, 41.9%; OR = 1.06; 95%CI: 0.89-1.25;  $P = 0.51$ ) (Figure 2). Statistically significant heterogeneity was not observed ( $I^2 = 45\%$ ,  $P = 0.51$ ).

### Adenoma detection rate

Five RCTs assessed the adenoma detection rate (ADR) ( $n = 2015$ ). The use of hyoscine demonstrated no statistically significant difference as compared to no hyoscine or placebo for ADR (294/1018, 28.9% *vs* 266/997, 26.7%; OR = 1.12; 95%CI: 0.92-1.37;  $P = 0.25$ ) (Figure 3). No heterogeneity was observed ( $I^2 = 17\%$ ,  $P = 0.25$ ).

### Timing of hyoscine administration

On subgroup analysis, hyoscine administration given at cecal intubation showed no statistically significant difference in polyp (467/1006, 46.4% *vs* 435/996, 43.7%; OR = 1.12; 95%CI: 0.94-1.34;  $P = 0.22$ ) or adenoma detection rate (287/948, 30.3% *vs* 256/934, 27.4%; OR = 1.15; 95%CI: 0.94-1.41;  $P = 0.17$ ) as compared to no hyoscine or placebo. Furthermore, hyoscine administration pre-procedure showed no difference in PDR (35/159, 22% *vs*

43/150, 28.7%; OR = 0.71; 95%CI: 0.42-1.19;  $P = 0.19$ ).

### Publication bias

Publication bias was not observed as measured with funnel plot, Egger's regression intercept method, or Begg-Mazumdar rank correlation method (Figure 4).

## DISCUSSION

CRC is a preventable and curative condition if diagnosed early in the premalignant polyp stage. The quality of colonoscopy is very important as many polyps may be missed during screening colonoscopies which can lead to the development of interval carcinoma at a later stage<sup>[33]</sup>. Currently, ADR is considered one of the core parameters of a quality screening colonoscopy and better ADR can lead to decreased incidence of interval carcinoma<sup>[34]</sup>.

Different medications including glucagon<sup>[18]</sup>, dicyclomine<sup>[19]</sup>, and atropine<sup>[20]</sup> have been tried to facilitate the colonoscopic exam with no significant improvement in results. Of all these agents, hyoscine has been evaluated extensively in RCTs with conflicting outcomes. Lee *et al*<sup>[17]</sup> found better PDR with the use of hyoscine with significant decrease in the colonic spasm. They did not notice any difference between the sites of polyps and suggested that hyoscine might be an option in patients with significant spasm<sup>[17]</sup>. Similarly, Corte *et al*<sup>[25]</sup> favored the use of hyoscine for screening and surveillance colonoscopy to aid in polyp detection. They did notice a difference in the withdrawal time and attributed that likely to the time spent on waiting for the spasm to resolve<sup>[25]</sup>. However, this was not designed primarily for ADR and considered

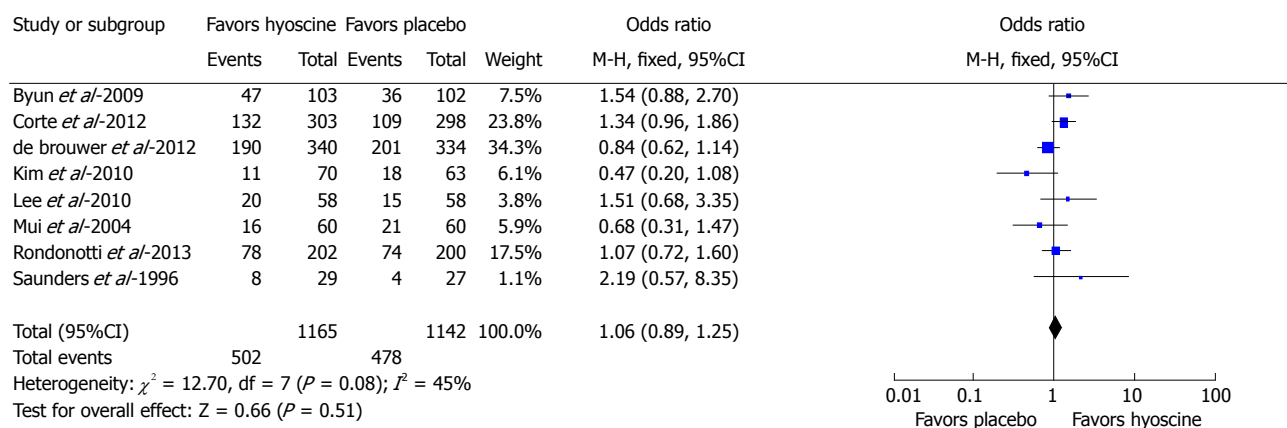


Figure 2 Forest plot showing no statistically significant difference in polyp detection rate between hyoscine and placebo group.

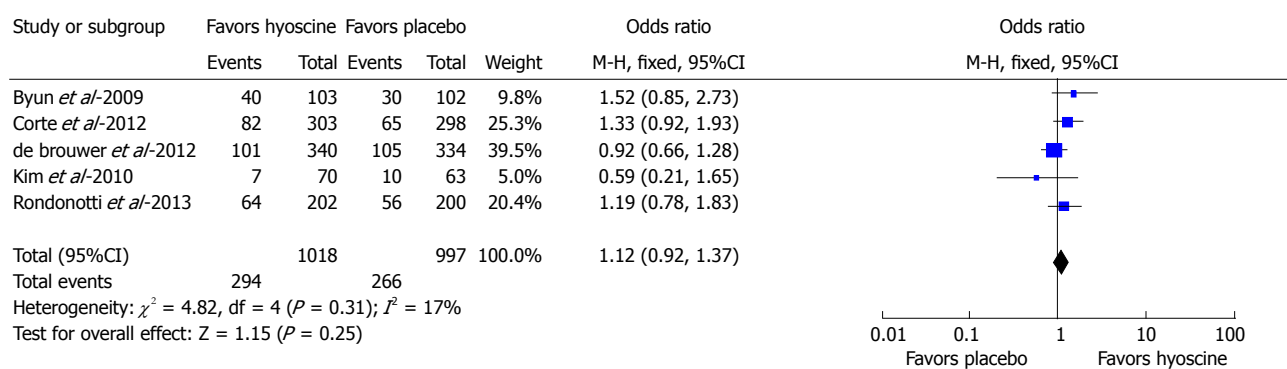


Figure 3 Forest plot showing no statistically significant difference in adenoma detection rate between hyoscine and placebo group.

PDR to be a surrogate marker for adenoma detection<sup>[25]</sup>. Despite these studies favoring the use of hyoscine to facilitate colonoscopy and polyp detection, other studies have showed contradictory results.

Byun *et al*<sup>[24]</sup> discovered no difference in polyp or ADR with more side effects with hyoscine use. Furthermore, procedure time and spasm score were not affected<sup>[24]</sup>. Similarly, de Brouwer *et al*<sup>[26]</sup> found no difference in PDR, ADR, or advanced lesions (> 1 cm) between the two groups. They did not appreciate any difference in withdrawal time between the two groups either but their study included gastroenterologists with more than 10-years' experience<sup>[26]</sup>. More recently, Rondonotti *et al*<sup>[29]</sup> found similar results in a well-designed randomized controlled trial with no differences in ADR or advanced adenomas. Their findings rather opposed the use of hyoscine because of the lower detection of flat lesions with no difference in the procedure tolerance between the two groups<sup>[29]</sup>. Given that the results are conflicting and the high impact on performing a better colonoscopic exam, this meta-analysis was conducted.

An ideal antispasmodic agent should be able to decrease the total procedure time with better procedure tolerability, acceptable side effect profile, and should increase the polyp and adenoma detection rate. Although hyoscine is considered a relatively safe medication<sup>[35,36]</sup>, Marshall *et al*<sup>[21]</sup> reported patients who developed sinus

tachycardia with hyoscine. Similarly, Rondonotti *et al*<sup>[29]</sup> also reported an increased incidence of tachycardia in the hyoscine group. The finding of tachycardia in these studies lead to unblinding. Byun *et al*<sup>[24]</sup> also reported significant incidence of dry mouth with the use of hyoscine.

In this meta-analysis, hyoscine use did not show an increase in PDR or ADR during colonoscopy. No statistically significant differences between hyoscine *vs* no hyoscine or placebo in adenoma or polyp detection irrespective of timing of hyoscine administration (given at cecal intubation or pre-procedure). Recently, Cui *et al*<sup>[37]</sup> found similar results with a meta-analysis on this subject; however, it was limited to only five studies. Numerous strengths were apparent in this meta-analysis. First, a three-stage extensive article and abstract search was carried out. Second, various populations with a large number of patients were included. Third, the two main outcomes (adenoma and polyp detection) were evaluated in all included studies. Fourth, inclusion of high-quality positive and negative RCTs as evaluated by the Jadad score. Finally, publication bias was not observed. Despite the strengths, a few limitations are observed in our meta-analysis. First, timing of administration of hyoscine was different in these studies with some administering it as premedication while others gave it after cecal intubation (Table 1). Therefore, a subgroup analysis was performed to evaluate if timing made a difference and discovered



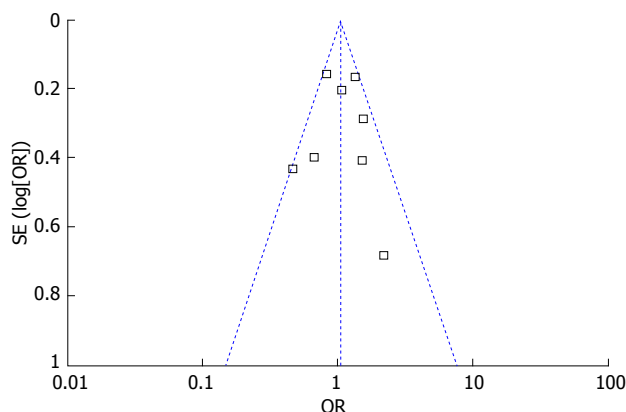


Figure 4 Funnel plot demonstrating no significant publication bias.

that timing did not impact the results. Second, Mui *et al*<sup>[28]</sup> used a slightly higher dose (40 mg) compared to other studies. However, if this study was removed, the results were unchanged. Third, Kim *et al*<sup>[27]</sup> administered hyoscine intramuscularly which may have a slightly different bioavailability compared to IV form. Again, when this study was removed, no changes were observed in the outcomes.

In conclusion, hyoscine use during colonoscopy does not increase the polyp or adenoma detection rate. Therefore, hyoscine should not be routinely used in an effort to increase polyp detection during colonoscopy.

## COMMENTS

### Background

The main purpose of colonoscopy is to identify adenomatous polyps and colorectal cancers. Given potential of colonic spasms during colonoscopy, many agents have been studied to decrease the spasms in an effort to improve the adenomatous detection rate (ADR). One such agent is hyoscine.

### Research frontiers

Hyoscine has been studied by multiple randomized controlled trials as an adjunct medication before or during colonoscopy to enhance ADR.

### Innovations and breakthroughs

The authors found that hyoscine administered before or during colonoscopy does not appear to improve polyp detection rate (PDR) or ADR.

### Applications

This information may limit the use of hyoscine before or during colonoscopy.

### Terminology

Odds ratio: Statistical term for the odds an event did or did not occur. Heterogeneity: Test for uniformity in composition of studies included. Publication bias: Phenomenon where positive studies are more published more than negative studies, leading to possible misrepresentation of data in meta-analysis. PDR: Having one or more polyps identified during a colonoscopy. ADR: Having one or more adenomatous polyps identified on colonoscopy.

### Peer review

The manuscript focussed on hyoscine for polyp detection during colonoscopy. The manuscript is well written.

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