

Effect of Hyoscine N-Butylbromide on Polyp Detection During Colonoscopy: A Meta-Analysis of Randomized Controlled Trials

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RESULTS: Five randomized controlled trials (RCTs) incorporating 1006 subjects in the Buscopan-group and 992 subjects in the placebo-group were included in this meta-analysis. We found no significant difference between these two groups in polyp detection rate (PDR) (RR 1.05, 95% CI:0.95-1.15, $P=0.33$), the adenoma detection rate (ADR) (RR 1.09, 95% CI:0.94-1.26, $P=0.24$), the advanced adenoma detection rate (A-ADR) (RR 0.91, 95% CI:0.66-1.25, $P=0.57$), the mean number of polyp detected per patient (MPP) (weighted mean difference $p=0.35$, 95% CI:-0.05-0.13, $P=0.35$), and adverse events-Tachycardia (RR 4.94, 95% CI:0.86-28.33, $P=0.07$).

CONCLUSION: Buscopan administered intravenously at time of cecal intubation does not improve PDR, ADR, A-ADR, and MPP, according to the five analyzed studies. The drug doesn't lead to obvious adverse events. Further research is required to determine whether the decrease in colonic spasms would affect polyp detection, and which specific patient populations may benefit from buscopan administration.

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Key words: Adenoma detection rate; Advanced-adenoma detection rate; Mean number of polyps detected per patient; Polyp detection rate

ABSTRACT

AIM: Colonoscopy is widely used to detect and remove adenomatous polyps. The missing rate of polyp using colonoscopy to detect colorectal diseases is significantly high. It is still controversial whether the use of antispasmodic drug hyoscine N-butylbromide (Buscopan) would enhance polyp detection using colonoscopy.

METHODS: In order to evaluate the efficacy and safety of antispasmodic drug hyoscine N-butylbromide in the detection and removal of adenomatous polyps using colonoscopy, we conducted a comprehensive strategy across various databases, and performed a meta-analysis on selected studies, according to the Cochrane

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world, and is one of the leading causes of cancer-related death^[1]. To our knowledge, CRC develops via the adenoma-carcinoma sequence, therefore, detection and removal of colonic

polyps at an early stage can decrease the incidence of colorectal cancer^[2]. Therefore, detection and removal of colonic polyps at an early stage can decrease the incidence of colorectal cancer.

Screening programs detecting early colonic neoplasia have been widely accepted in the last two decades. Colonoscopy has been a key technique for colorectal cancer (CRC) screening, and it is to date the best available method to detect and remove colonic polyps. Thus, colonoscopy serves as the gold standard in identification and removal of colonic polyps^[3]. However, polyp miss rates during colonoscopy, as determined by meta-analysis and population-based studies, have been reported around 5-22%^[4,5]. Such a high percentage is thought to reflect multiple factors including bowel preparation, effective use of sedation, polyp position, withdrawal techniques, and the technology used for the detection. In addition, colonic spasm, which is a relatively common problem that has not been adequately studied yet, may affect the mucosal surface, as well as the adenoma detection rate.

The anticholinergic drug buscopan is a smooth muscle relaxant that is used to reduce gastrointestinal spasm. It has a good safety profile, and its adverse effects (mild xerostomia, mydriasis, and tachycardia) are unusual. The use of antispasmodic drugs has been frequently employed in gastrointestinal endoscopy, based on the hypothesis that it could flatten the haustral folds via reducing the muscular tone, therefore increasing the mucosal view. According to a survey recently, up to 85.6% of the colonoscopists sometimes or always use hyoscine assessing the current use of hyoscine among UK^[6]. But recent studies have provided controversial results on the effects of antispasmodic agents in colonoscopy. For example, de Brouwer EJ *et al*^[7] conducted a RCT and came to the conclusion that buscopan could not improve polyp detection during colonoscopy, however, study from Corte C *et al*^[8] reported the opposite results that buscopan improved polyp detection. In addition, no systemic review has addressed these questions to date, here, we performed a meta-analysis of eligible RCTs to evaluate the efficacy and safety of buscopan, aiming to provide the scientific evidence to determine whether its routine use is reasonable, and should be recommended in the future routine practice.

METHODS

Search strategy

We performed a systematic search using the databases: The Cochrane Library, PubMed (1994 to December 2013), Embase (1974 to September 2013), Web of Science (1960 to December 2013), and CBMdisc (1978 to December 2013), without language restriction and with the following search terms: buscopan polyp detection, adenoma detection, and colonoscopy. A recursive manual search of cited references in published studies was performed to identify additional articles. Abstracts of important gastrointestinal meetings, such as “American College of Gastroenterology” meetings and “Digestive Disease Week” were also systematically searched.

Selection of studies

Inclusion criteria were: (1) Study design of the articles were randomized controlled trials (RCTs) evaluating whether buscopan administration can exert influence on the polyp detection rate; (2) Patients referred for either diagnostic or screening colonoscopy; (3) The study medication was given intravenously; (4) Parameter evaluated in each study: Polyp detection rate (PDR), adenoma detection rate (ADR), advanced- adenoma detection rate (A-ADR), mean number of polyps detected per patient (MPP) and adverse

events (Tachycardia); (5) In case of repeated reports, only the latest version was chosen.

Exclusion criteria were: (1) Commentaries, case reports, reviews, or guideline articles; (2) Antispasmodic agents were given as a pre-medication before colonoscopy; (3) Articles not providing enough data for the meta-analysis were excluded.

Data extraction and study quality assessment

Identified studies were reviewed independently by two different researchers, and then reciprocally verified to determine whether they were meeting the inclusion criteria for this meta-analysis. For studies fulfilling the inclusion criteria, two authors independently extracted the first author, year of publication, number of participants in each group, baseline consistency and the primary and secondary endpoints in each included study. Then, relevant data were extracted for further analysis. Any disagreement in either study selection or data extraction was made a consensus decision by further discussion, in order to avoid any bias.

The methodological quality of each study was assessed according to standard data-extraction templates. We used the following domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective outcome reporting, and other bias. Judgments towards the included studies were categorized as ‘Low risk’, ‘High risk’ or ‘Unclear risk’ of bias, as described in the latest Cochrane Handbook (version 5.1.0) for Systematic Reviews of Interventions.

Evaluation criteria for endpoints

Primary end points: (1) PDR (direct indicator of the procedure), defined as the percentage of colonoscopies in which at least one polyp was found; (2) ADR (widely used as the key indicator of colonoscopic quality), defined as the proportion of colonoscopies in which at least one adenoma was identified in the subject; (3) A-ADR, defined as the percentage of colonoscopies in which at least one adenoma was found (with polyps >1 cm that had villous architecture, high-grade dysplasia, and carcinoma in situ, or overt carcinomas).

Secondary end points: (1) MPP, defined as the mean number of polyps detected per patient during the procedure; (2) Adverse events (Tachycardia, defined as pulse rate >100 beats/min)

Statistical analysis

Statistical analyses were performed according to the statistical guideline referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions. The meta-analysis was conducted with RevMan 5.2 software (Cochrane Collaboration). The weighted mean difference was recommended for continuous data, and the risk ratio (RR) with 95% confidence intervals (CI) was used for dichotomous data in the intervention study. Heterogeneity among the studies was assessed by the chi-square test, and a significance level of an equal to 0.1. In view of the low power of such tests, heterogeneity with the I^2 statistic, in which I^2 values of 50% or more was indicating a substantial level of heterogeneity was also performed. Meta-analysis was calculated using a fixed-effects model when no heterogeneity was detected. If any heterogeneity existed, subgroup analysis or a random-effects model was performed. A sensitivity analysis was also conducted to estimate the influence of each study on the overall results, by repeating the meta-analysis while omitting one study at a time. Because of the limited number of RCTs, we did not carry out funnel plot analysis.

RESULTS

Study inclusion and assessment

Our search strategy yielded a total of 271 potential studies (Figure 1). Of the 21 potential randomized controlled trials, 16 were excluded for the following reasons: buscopan was given as premedication intravenously (four RCTs^[9-12]); buscopan effects were evaluated in retrograde ileoscopy (one RCT^[13]); the antispasmodic agent was administered via sublingual hyoscyamine spray and not injected intravenously (two RCTs^[14,15]); meperidine and buscopan were compared during colonoscopy (one RCT^[16]); hyoscyamine-sulphate, -dicyclomine or -hydrochloride were used (three RCTs^[17-19]); the chemical structure of the used drug was different from buscopan. Interim analysis^[20] containing the same data in two different conference meeting, only the terminal article was included (one RCT^[8]). From the remaining 5 RCTs (4 full texts and 1 abstract), a total of 1998 patients were enrolled in the meta-analysis, including 1006 in the buscopan -group (Buscopan-group) and 992 in the placebo-group. The main characteristics and bias of all the five studies are listed in table 1 and table 2, respectively.

Comparison of effect

PDR: Five^[7,8,21-23] studies (1998 patients) reported polyp detection rate in the Buscopan-and the placebo-group. There was no heterogeneity among the studies ($P=0.19$; $I^2=35\%$), so a fixed-effects model was applied. Data demonstrated that there was no significant difference in the Buscopan-group (467/1,006) compared to the placebo-group (439/992) (RR 1.05,95% CI:0.95-1.15, $P=0.33$) (Figure 2). The study^[22] with the smallest sample size was excluded, and sensitivity analysis was performed. Results showed no difference of polyp detection rate between the two groups (RR 1.04, 95% CI, 0.94-1.14; $P=0.44$); moreover, there was no significant heterogeneity ($P=0.15$; $I^2=43\%$).

ADR: Four^[7,8,21,23] studies provided adenoma detection rate data. From a total of 1882 patients, 283/948 subjects in the Buscopan-group and 256/934 patients in the placebo-group were positive for at least one adenoma, respectively. There was no statistical heterogeneity across the studies ($P=0.47$, $I^2= 0$), so a fixed-effects model was used. Results showed no benefit from the use of buscopan

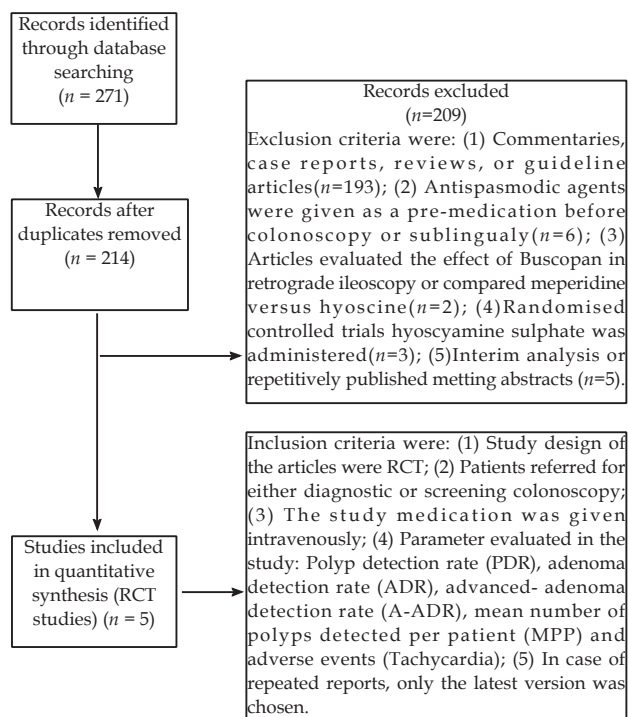


Figure1 Flow chart for how the published RCTs (Randomized Controlled Trials) are selected from the literature for this meta-analysis of ‘Effect of Hyoscine N-butylbromide on polyp detection during colonoscopy: a meta-analysis of randomized controlled trials’.

on adenoma detection rate (RR 1.09, 95% CI:0.94-1.26, $P=0.24$) (Figure 3).

A-ADR: Only two^[7,21] studies reported advanced- adenoma detection rate in the Buscopan- and the placebo-group. There was no heterogeneity among the studies ($P=0.35$; $I^2=0$), so a fixed-effects model was applied. Result demonstrated that there was no significant difference in the Buscopan- (64/542) versus the placebo-group (69/534) (RR 0.91,95% CI:0.66-1.25, $P=0.57$) (Figure 4). The pooled data showed no increase in the advanced-adenoma detection rate in the Buscopan -group.

Table 1 Characteristics of included RCT (Randomized Controlled Trials) studies in the meta-analysis of ‘Effect of Hyoscine N-butylbromide on polyp detection during colonoscopy: a meta-analysis of randomized controlled trials’.

Author	Year	Country	Patients	Full text/Abstract	Baseline consistency	Study endpoints
Buyn TJ	2009	Korea	Buscopan: 103 Placebo: 102	Abstract	Not recorded	PDR, ADR, vital signs, side effect
de Brouwer EJ	2012	Netherlands	Buscopan: 340 Placebo: 334	Full text	Yes	PDR, ADR, A-ADR, MPP
Rondonotti E	2013	Italy	Buscopan: 202 Placebo: 200	Full text	Yes	PDR, ADR, detection rate of flat/depressed lesion, side-effects
Corte C	2012	Australia	Buscopan: 303 Placebo: 298	Full text	Yes	PDR, ADR, MPP
Lee JM	2010	Korea	Buscopan: 58 Placebo: 58	Full text	Yes	PDR, insertion time, MPP, site/size/shape of polyps,vital signs

Table 2 Bias of included RCT (Randomized Controlled Trials) studies in the meta-analysis of ‘Effect of Hyoscine N-butylbromide on polyp detection during colonoscopy: a meta-analysis of randomized controlled trials’.

Study	Random Sequence Generation	Allocation Concealment	Blinding (Participants +Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome data	Selective Reporting	Other bias
Buyn TJ	unclear	unclear	unclear	unclear	low	low	unclear
de Brouwer EJ	unclear	low	low	low	low	low	low
Rondonotti E	low	low	high	low	low	low	low
Corte C	low	low	low	low	low	low	low
Lee JM	low	low	low	low	low	low	low

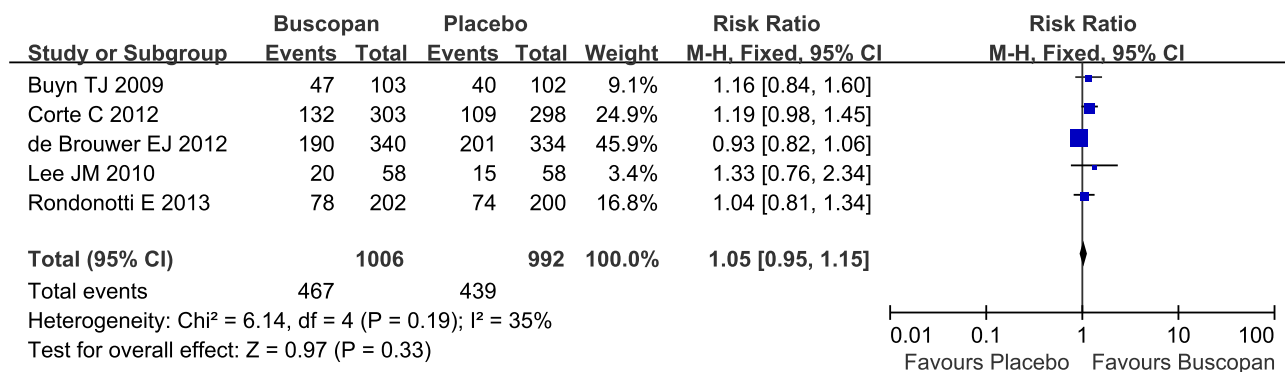


Figure 2 Polyp detection rate in the Buscopan-and placebo-group.

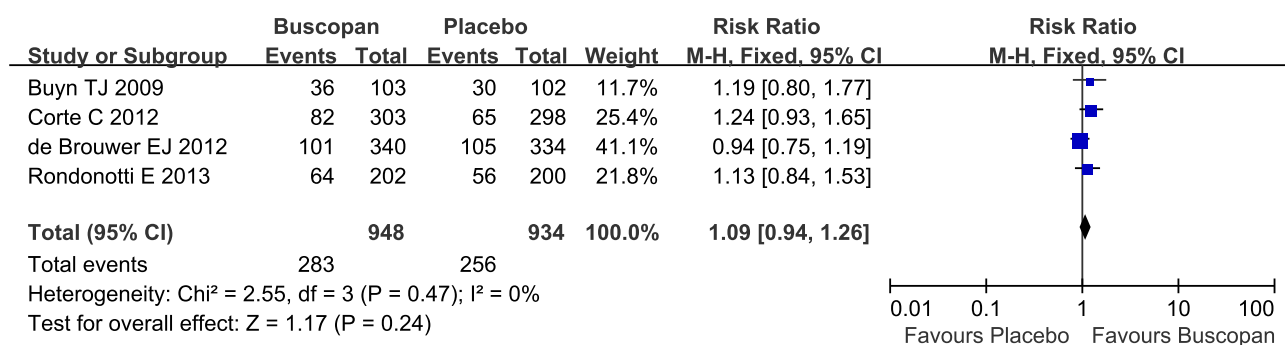


Figure 3 Adenoma detection rate in Buscopan-and placebo-group.

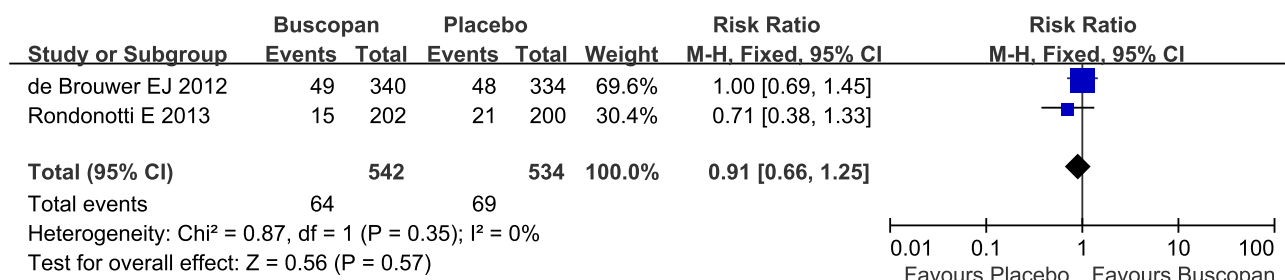


Figure 4 Advanced-adenoma detection rate in Buscopan-and placebo-group.

MPP: Four^[7,8,21,22] studies provided the mean number of polyps detected per patient, but only three of them^[8,21,22] were included in the quantitative analysis because one^[7] study provided no standard deviation (SD) -standard error (SE) values. It should be noted that standard error (SE) was reported in 1 study^[20], even so, we transform it into SD through the formula $SE=SD/\sqrt{n}$. There was no heterogeneity among the studies ($P=0.34$, $I^2=7\%$), so a fixed-effects model was applied. There was no significant difference in the Buscopan - versus the placebo-group (weighted mean difference 0.13, 95% CI: -0.04-0.30, $p=0.13$) (Figure 5).

Adverse events-Tachycardia: Most of the studies showed a good safety profile and demonstrated low adverse event rates. However, four^[7,8,21,22] studies reported that administration of an antispasmodic drug caused tachycardia in some patients (total of 1,793). There was no heterogeneity among the studies ($P=0.72$; $I^2=0\%$), so a fixed-effects model was applied. Result demonstrated no significant difference in the Buscopan-group (7/505) versus the placebo-group (1/498) (RR 4.94, 95% CI 0.86-28.33; $P=0.07$) (Figure 6).

DISCUSSION

Colorectal cancer screening can reduce mortality through the detection of early-stage adenocarcinomas and the removal of precursor adenomatous polyps. Adenoma detection rate has been widely used as the most important indicator of colonoscopic quality that correlates with subsequent cancer risk; therefore, improving adenoma detection rate or polyps detection is a must for colorectal cancer prevention. A wide selection of antispasmodic drugs has been routinely used during colonoscopy both in the US healthcare practice and among different countries. However to date, results remain conflicting, with no validation of clinical benefits.

In this study, we performed a meta-analysis including five RCTs (4 full texts and 1 abstract), incorporating a total of 1998 subjects (1006 subjects in the buscopan-group and 992 subjects in the placebo-group). Pooled data provided no evidence that administration of buscopan improved detection of neoplastic lesions. In addition, no statistically significant difference in other studyendpoints was demonstrated.

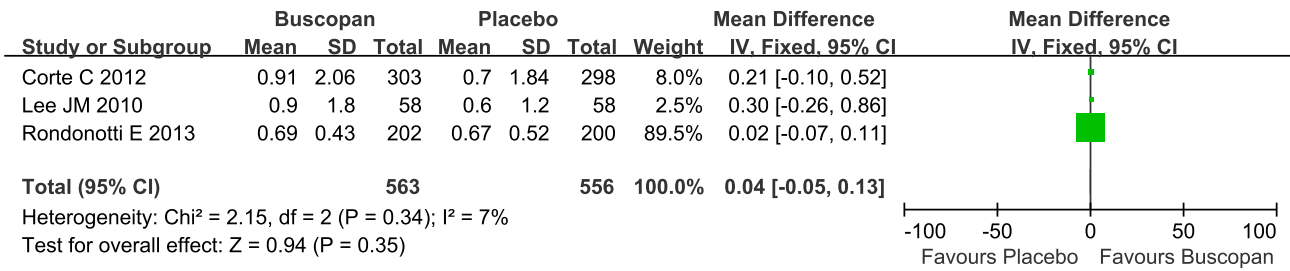


Figure 5 Mean number of polyps detected per patient in Buscopan-and placebo-group.

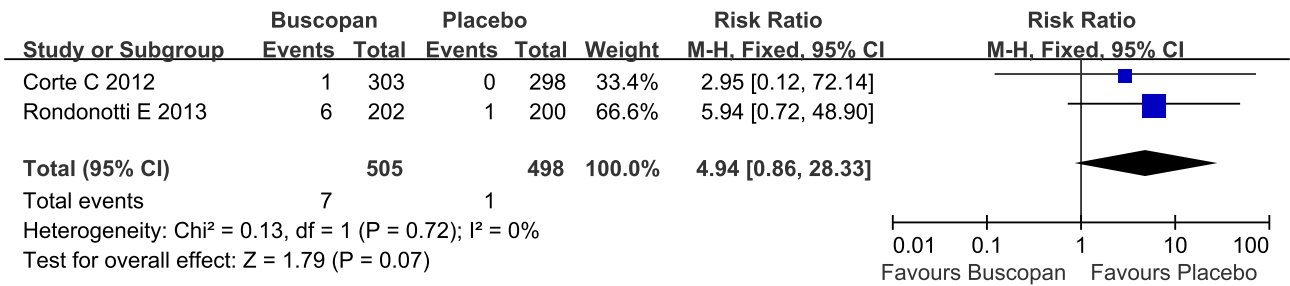


Figure 6 Tachycardia in Buscopan-and placebo-group.

There are several strengths presenting in this meta-analysis, we excluded other non-RCTs related studies and analyzed five RCTs with objective assessments of the methodological quality of each study, which was conducted according to the standards established by the Cochrane Handbook (version 5.1.0). All the eligible studies underwent an intention-to-treat analysis in terms of PDR, ADR, A-ADR. Comprehensive qualities of the included studies were relatively high, with seven domains assessing the risk of bias almost all with low risk (only few with high risk were evaluated, except some detailed information in one included abstract that could not be acquired completely). Detailed information of the included studies in the meta-analysis is shown in table 2.

Concerning to ADR (the gold standard for colonoscopy quality indicators), Corte C and colleagues *et al*^[8] has recently shown that the adjusted odds of detecting any adenoma were 1.62 times higher in the Buscopan- versus the placebo-group, indicating that Buscopan treatment may be helpful in improving PDR when conducting a multivariate analysis. In addition, a landmark study^[24] from Poland focused on the relationship between interval cancer and ADR as colonoscopic quality indicator, has demonstrated that the risk of interval cancer was significantly higher among subjects who underwent colonoscopies with ADR less than 20%, than among subjects with ADR of 20% or more. To this respect, studies on the administration of buscopan would be helpful to determine its clinical significance on survival rates.

Lee and coworkers^[22] have shown that the administration of buscopan has led to the identification of 10/40 subjects with at least one adenoma as compared to 3/42 subjects in the placebo-group, respectively (25.0% vs 7.1%, P=0.06). the trend implied that buscopan might play a role in increasing ADR in patients with colonic spasms; however, such result would need confirmation by specific studies focused on this subgroup of patients, because this subgroup of the patients is small. Concerning the effect of buscopan in the detection of flat/depressed lesions between the two groups^[21], a significantly lower detection rate of lesions has been found in the buscopan group versus the placebo-group (0.5% vs 5.5%, P=0.003). These results suggest that more attention should be paid onto the

negative influence of buscopan on the detection of such lesions. We speculate that the lower detection rate could somehow depend on the flattening of haustral folds, which makes these lesions even less detectable. Further studies are needed in order to establish whether patients may benefit from buscopan administration, and eventually which patient population the administration would be targeted to. In addition, concerns should also be raised on the indiscriminate use of buscopan during colonoscopy in the routine practice, which would increase the development of flat/depressed lesions.

A variety of other antispasmodic agents during colonoscopy have been investigated to date, however the conclusions are conflicting. Recently, a randomized placebo-controlled trial^[25] compared the effectiveness of glucagon in colonoscopy under the current equipment settings. Data suggested that the cecal intubation time is significantly shorter in the glucagon-group compared to the control-group, but PDR values were not significantly different between the treated and placebo-group. This study also implied that the routinely practice of colonoscopy with medication aids should be carefully evaluated for the potential resulting side-effects.

However, there are some limitations. First, colonoscopist-related factors could introduce heterogeneity among the included studies. Secondly, pre-medication and simultaneous sedative- and analgesic-treatments may alter the effect of antispasmodic drugs (drug dosage within the selected studies was not exactly the same, and this potentially confounding factor was not taken into account). In addition, not all of the studies conducted the intention-to-treat analysis, which may result in the risk of bias for the incomplete outcome data to a certain extent. Finally, four of the five included studies were single-center designed but one study was conducted in two centers (a university hospital and an associated endoscopy clinic).

In conclusion, this meta-analysis showed no evidence that the routine use of buscopan would improve PDR, ADR, A-ADR, and MPP. Therefore, the potential impact of antispasmodic drugs on ADR should be assessed in properly designed, prospective, randomized, double-blind, placebo-controlled studies at a larger scale. More work is needed before antispasmodic drugs can be used in a standard cost-effective practice to enhance the sensitivity of colonoscopy for polyp detection.

List of abbreviations

ADR: adenoma detection rate;
 A-ADR: advanced- adenoma detection rate;
 MPP: mean number of polyps detected per patient;
 PDR: polyp detection rate;
 RCT: randomized controlled trial;
 IBS: irritable bowel disease.

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