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ORIGINAL ARTICLE

The role of routinely given hyoscine-N-butylbromide in colonoscopy: a double-blind, randomized, placebo-controlled, clinical trial

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ABSTRACT

Objective: Hyoscine-*N*-butylbromide (HBB) has been proposed to ease colonoscopy and improve mucosal visualization, yet the results from previous studies are conflicting. In our prospective, double-blind, placebo-controlled, randomized study we aimed at evaluating whether routine administration of HBB, before and during colonoscopy, ease the procedure or increase the detection rate for polyps. *Material and methods*: One hundred fifty outpatients scheduled for an elective colonoscopy were randomized to receive intravenous injections of either 10 mg hyoscine-*N*-butylbromide or saline before insertion and at cecum. Patient tolerance and technical ease of colonoscopy were evaluated by visual analogue scale (VAS). Procedure times were recorded. Number of detected polyps per patient was evaluated as well. Heart rate was monitored with a pulse oximetry. *Results*: HBB did not improve patient tolerance or technically ease the procedure as evaluated by VAS. However, HBB led to faster ileal intubation (1.5 vs 2.0 min, $p < 0.001$) and shorter total procedure time (22.0 vs 24.0 min, $p = 0.03$). Patients who received HBB also needed less often external abdominal pressure (48.6 vs 66.7%, $p = 0.03$). HBB did not improve polyp detection rate (0.89 vs 0.91, $p = 0.90$). HBB induced a significant rise in heart rate ($p < 0.001$) and more often tachycardia (17.6 vs 0%, $p < 0.001$). *Conclusions*: Routine administration of HBB before and during colonoscopy yields only limited improvement in the technical performance of the examination compromised by high incidence of tachycardia.

KEYWORDS
Colonoscopy, scopolamine hydrobromide, pain, polyps

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Introduction

Colonoscopy is the gold standard for the diagnosis and treatment of colonic diseases. In addition, colonoscopy with adenoma detection and endoscopic removal can prevent colorectal cancer [1]. Hence, screening programs to detect early colonic neoplasia are implemented. However, colonoscopy may be a challenging procedure for the endoscopist as well as for the patient. Colonic spasm may impede colonoscope insertion leading to a prolonged and difficult procedure causing discomfort and pain in the patient. Colonic contractility may also hamper visibility of mucosal pathology. Therefore, it is a common practice in many endoscopy units to alleviate colonoscopy by administering an antispasmodic agent, hyoscine-*N*-butylbromide (HBB), before insertion of the colonoscope [2–4]. It has also been proposed that HBB might improve visualization of colonic mucosa by inducing colon relaxation [5]. Use of HBB has been even used as a quality indicator for colonoscopy [6].

In terms of alleviating insertion of the endoscope and patient discomfort the benefit of routine use of an antispasmodic agent has remained controversial. Many endoscopists believe that reduced colonic muscle tone may actually make colonoscopy even more difficult [7]. A reason for controversial results of previous studies may be the heterogeneity and even flaws in the study settings: many endoscopists with variable experience in relatively small patient populations, variable use of sedative medication, and different spasmolytic agents with various doses and routes as well as timing of drug administration. The anticholinergic properties of spasmolytic drugs inducing tachycardia has also risen safety concerns [8]. The adenoma detection rate (ADR) has been shown to correlate with subsequent cancer risk [9]. Improving ADR is one of the key challenges in gastroenterology today. Administering HBB during withdrawal of the colonoscope has been proposed to increase ADR [10,11].

In this randomized, placebo-controlled prospective study we evaluated the impact of HBB (Buscopan®;

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Boehringer Ingelheim, Germany) on patient tolerance and technical difficulty of colonoscopy as well as the polyp detection rate. We compared two groups of unsedated patients; one group treated with intravenous (i.v.) HBB, the other with i.v. saline.

Materials and methods

The study was conducted at Laakso Hospital, Helsinki, Finland. Initially, 218 outpatients were scheduled for diagnostic colonoscopy fulfilling the eligibility criteria on the basis of the referral were recruited. The eligibility criteria included age between 45 and 75 years, ability to complete a questionnaire, and no history of intolerance to HBB. Patients on anticholinergic medication including tricyclic antidepressants and selective serotonin reuptake inhibitors or with a history of colonic resection, serious comorbidity, e.g. severe cardiac or pulmonary disease, arrhythmias, drug abuse or alcoholism, glaucoma, obstructive uropathy or active inflammatory bowel disease were excluded. Desire to undergo colonoscopy with sedation was an exclusion criteria as well. However, sedation on-demand as well as HBB during colonoscopy as a rescue therapy was left to the discretion of the endoscopist.

A standard bowel preparation with polyethylene glycol (Moviprep®, Norgine Limited, Hengoed, Great Britain) was used. Sixty-eight patients either declined participation or were excluded after medical interview, because they did not meet the eligibility criteria. Thus, 150 outpatients entered the study between March 2012 and March 2014. All patients signed informed consent. The patients were randomized in blocks of six by opening a sealed envelope to receive either HBB (HBB group) or saline (placebo group) i.v. The envelopes had been coded and sealed by a person not attending the trial in any other way. The study protocol was approved by the local ethical committee and is in accordance with the Helsinki Declaration.

An injection of 10 mg (0.5 ml) HBB or an equivalent volume of saline was administered over 30–60 s three minutes before the introduction of the colonoscope. A supplemental dose of 10 mg HBB or saline was delivered when the tip of the colonoscope reached the cecum. Heart rate was monitored with a pulse oximetry. The injections were administered and the heart rate monitored by a nurse not attending the colonoscopic procedure. The endoscopist, the assisting endoscopy nurse and the patient were blinded to the treatment modality and heart rate monitoring.

All colonoscopies were performed by two experienced endoscopists (M.R. and H.K.-M.) using standard Olympus CF-H180AL and -DL colonoscopes (Olympus Optical Co., Ltd., Tokyo, Japan). No ScopeGuide feature of CF-H180DL colonoscopes was used. Biopsy and polypectomy with standard techniques were carried out if indicated. Sedation was given on demand with midazolam and fentanyl.

After the examination, the patients completed a questionnaire on the overall difficulty of the examination, the degree of abdominal pain and unpleasantness experienced during the procedure. The endoscopist evaluated the technical difficulty of the examination, the degree of pain experienced by the patient and bowel preparation. Answers were given on a 100 mm visual analogue scale (VAS). The distance from the left endpoint (in millimeters) quantified the variable. The left end of the scale (0 mm) was defined as ''not at all'' and the right end (100 mm) as ''extremely''. Bowel preparation was graded with VAS (0 mm = extremely poor, 100 mm = perfect). The number of detected polyps was recorded excluding the small (<5 mm), macroscopically typical hyperplastic polyps at the rectosigmoid location. Whether the assistant had to apply hand pressure to the abdomen to facilitate the insertion was recorded. Patients were also asked to indicate whether they were willing to repeat the examination in the future; 1 = without hesitation, 2 = only if necessary or 3 = not under any circumstances.

The time required to enter the cecum and the ileum as well as the total procedure time were recorded. The use of standard biopsy forceps on withdrawal was included in the total procedure time. Nevertheless, the time required to perform a polypectomy with a snare or any other additional procedures during the examination was subtracted from the total procedure time. Heart rate before insertion of intravenous cannula, before insertion of the colonoscope, and maximum heart rate during the examination was recorded. Tachycardia was defined as heart rate $\geq$120 bpm. The time of ileal intubation was measured from the point the tip of the endoscope reached the cecum till it entered the ileum.

Patient tolerance was the primary endpoint. Assuming that a difference of 15 mm in VAS evaluation is clinically relevant [12,13], the sample size was calculated to provide 95% power for detecting a difference between two groups at 0.05 significance level. A standard deviation of 23 mm was assumed [12]. The minimum sample size required was 65 patients per treatment group. VAS measures were analysed using group means as continuous variables. After testing normality of distribution the continuous variables were compared with independent samples Mann–Whitney U test or T test, when appropriate. The heart rates within the groups were tested by Wilcoxon signed ranks test. Categorical variables were compared with the

chi-squared test. The level of statistical significance was defined as $p < 0.05$. The results are given as mean ± SEM unless otherwise indicated. SPSS-package (version 21, SPSS Inc., Chicago IL) was used for all statistics.

Results

Seventy-five patients received HBB and 75 placebo. The demographic data of the study groups is presented in Table I. When analysing the data, one male patient in HBB group was found to take an anticholinergic agent on regular basis and was excluded from further analysis. In the case of one female patient in the placebo group a complete colonoscopy was unsuccessful due to severely rigid sigmoid colon. Her data concerning duration of the procedure or number of polyps was not included in the analysis. Hence, complete colonoscopy was achieved in 99.3% of patients. Of those terminal ileum was intubated in 97% of patients in the HBB and in 96% in the placebo group ($p = 0.65$). In case of one female patient receiving HBB passing a rigid sigmoid colon with a colonoscope was hindered. Switching over to a gastroscope resulted in a complete colonoscopy. Her data is included in the analysis. During withdrawal two patients (both in the HBB group) were given HBB as a rescue therapy due to severe spasms in the sigmoid colon. Sedation during the examination was given to three and seven patients in the HBB and placebo groups, respectively ($p = 0.3$). Bowel preparation was similar in the study groups (Table II). No patient was excluded owing to poor bowel cleansing.

Figure 1 displays the patients' and the endoscopists' assessments on colonoscopy. Administering HBB did not alleviate the overall difficulty of the examination ($p = 0.24$), abdominal pain ($p = 0.27$) or the degree of unpleasantness ($p = 0.13$) experienced by the patient. Neither had drug administration a statistically significant effect on the endoscopists' ratings on the difficulty of the examination ($p = 0.16$) or patient's pain ($p = 0.35$). However, patients in the HBB group needed less frequently external abdominal pressure applied by the assistant during the procedure (48.6% vs 66.7%, $p = 0.03$). The time to reach cecum was comparable between the groups ($p = 0.11$) (Table II). However, total procedure time turned out to be shorter in the HBB group (22.0 vs 24.0 min, $p = 0.03$). It took 1.5 minutes to enter the ileum in the HBB group and 2.0 minutes in the placebo group ($p < 0.001$). Fifty-three patients in each study group agreed to repeat the examination without hesitation and only one patient in the HBB group refused to repeat it under any circumstances ($p = 0.58$).

HBB induced a significant rise in heart rate as compared to baseline value ($p < 0.001$) and the placebo

Table I. Patient characteristics.

	HBB group ($n = 75$)	Placebo group ($n = 75$)	p-Value
Age (years)	61.6 ± 8.2	59.8 ± 8.9	0.24
Gender (male/female)	37/38	30/45	0.25
Body mass index (kg/m^2)	26.5 ± 4.5	26.1 ± 4.1	0.56
Smokers (%)	15	21	0.31
Alcohol intake (gm/week)	69 ± 126	50 ± 63	0.44
Previous abdominal surgery (%)	46	61	0.097
Previous colonoscopy (%)	39	36	0.69
State of health			
No chronic disease (%)	39	32	0.39
Cardiovascular disease (%)	37	36	0.87
Diabetes (%)	12	8	0.41
Indication for colonoscopy			0.045
Altered bowel habit (%)	21	27	
Anemia or bleeding (%)	21	39	
Adenoma surveillance (%)	11	11	
Abdominal pain (%)	23	11	
Other (%)	24	13	

Values are mean ± SD or %.

Table II. Procedure characteristics.

	HBB group ($n = 74$*)	Placebo group ($n = 75$)	p-Value
Bowel preparation (VAS)	69 ± 2.6	70 ± 2.4	0.76
Findings at colonoscopy			
Normal (%)	10	13	0.46
Diverticulosis (%)	57	48	0.29
Polyps or tumors (%)	45	46	0.87
Hemorrhoids (%)	23	32	0.22
Inflammatory bowel disease (%)	3	4	0.66
Cecal intubation time (minutes)	9.3 ± 0.7	10.2 ± 0.6	0.11
Ileal intubation time (minutes)	1.5 ± 0.3	2.0 ± 0.2	<0.001
Total procedure time (minutes)	22.0 ± 0.8	24 ± 0.8	0.03

Values are mean ± SEM or %.
*One patient was excluded from the analysis because of the use of an anticholinergic drug.

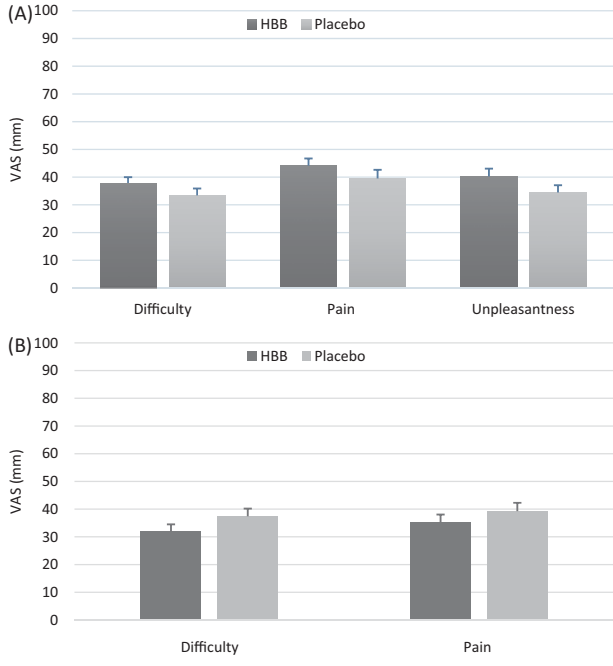

Figure 1. Effect of HBB on colonoscopy as assessed by the patient (A) and the endoscopist (B). The differences are not statistically significant. Values are VAS ratings +SEM.

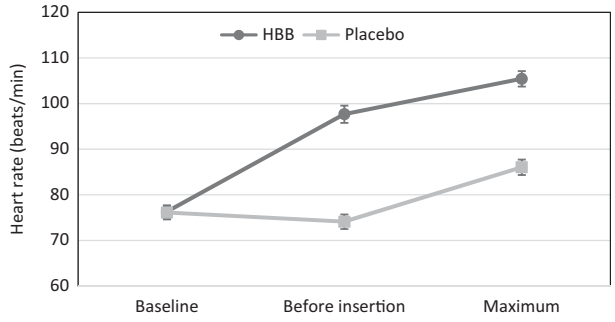

Figure 2. Heart rates (±SEM) before injection and before colonocope insertion as well as highest heart rate during colonoscopy. The differences between the groups before insertion and during colonoscopy were highly significant ($p < 0.001$). Colonoscopy induced a significant rise in heart rate compared to baseline values in both study groups ($p < 0.001$).

group ($p < 0.001$) (Figure 2). Thirteen patients in the HBB group (17.6%) experienced tachycardia while none receiving placebo (0%) ($p < 0.001$).

The mean number of polyps or tumours detected per patient in the HBB and placebo groups were similar (0.89 vs 0.91, $p = 0.90$). Accordingly, the number of patients harbouring a polyp or tumour was analogous (44.6% vs 45.9%, $p = 0.87$). One evident rectal cancer in both study groups were discovered.

Discussion

Colonoscopy is an invasive procedure which may be technically challenging for the endoscopist and difficult, or even painful for the patient. Administering an antispasmodic agent either at the beginning of colonoscopy to achieve a faster and easier examination [2,8,14,15] or during withdrawal to improve polyp detection rate [10,11] has been suggested. In this study, we demonstrated that 10 mg HBB given at the beginning and at cecum did not improve the patient's or endoscopist's satisfaction. However, it did reduce the need for external pressure to the abdomen, suggesting a technically easier procedure. Moreover, administration of HBB speeded up ileal intubation and decreased total procedure time. We did not find any improvement with HBB as it comes to polyp detection rate. HBB induced a marked rise in heart rate and episodes of tachycardia (≥120 bpm).

The rationale for administration of HBB before colonoscopy is to decrease motility which may hamper advancement of the colonoscope causing a difficult, prolonged, and painful examination. Indeed, in their placebo-controlled study with 56 patients, Saunders and Williams [2] reported that 20 mg HBB administered i.v. before colonoscopy resulted in a quicker intubation of the cecum, less colonic spasm and an easier examination as evaluated by the endoscopist but no benefit in patient's ratings. Similarly, Marshall et al. [8] found hyoscyamine sulphate 0.5 mg i.v. beneficial in terms of procedure time, ease of the examination and patient comfort. Even a 0.25 mg sublingual hyoscyamine spray 15–30 min before colonoscopy yielded improvement in difficulty and colonic motility scores, but only after adjustment for age and sex [14]. Sulu et al. [15] achieved faster cecal reach and total endoscopy time with HBB as compared to meperidine in the elderly population. Furthermore, HBB administration at time of cecal intubation to facilitate ileal intubation has been proposed [16,17]. However, the beneficial effect of antispasmodic agents is controversial. In two older studies [18,19] intramuscular dicyclomine hydrochloride or glucagon prior to the colonoscopy did not facilitate the examination. Subsequently, in the study by Waxman et al. [20], 0.5 mg atropine did not ease colonoscopy or improve patient tolerance. Similar findings were noted after administration of hyoscyamine (0.25 mg) either i.v. or orally 20–40 min before colonoscopy [21]. Neither was there any difference in insertion time to cecum compared to placebo. Paralleling these results, Yoong et al. [22] did not find significant improvement with HBB 20 mg i.v. on cecal intubation time or rate. Increasing the HBB dose to 40 mg has yielded even detrimental effects on cecal intubation time as well as patient's and endoscopist's satisfaction [7]. Similarly, glucagon 1 mg administered i.v. either before or during colonoscopy had no effect on procedure times [23]. However, this was challenged by a recent observation by Tamai et al. [24] who demonstrated that glucagon administered before colonoscopy improved patient tolerance, facilitated scope manipulation and decreased cecal intubation time.

Administering HBB at cecal intubation has given improved polyp detection rate in some studies [10,11]. However, the findings are controversial and in fact, three recent meta-analysis have concluded that the impact of HBB on polyp detection rate is small, if existent at all [25–27].

To our knowledge, this is the first randomized, placebo-controlled study addressing the effect of HBB on colonoscopy in unsedated patients. Sedation was given on demand resulting a 6.7% sedation rate (10 patients). Sedation may be a significant confounding factor when evaluating the effect of an antispasmodic drug [7]. Sedatives and analgesics may not only influence the anticholinergic properties of HBB, but in addition, variable levels of sedation make it difficult to

evaluate the true effect of HBB on the procedure. We chose to use the dose of 10 mg HBB prior to insertion and at cecal intubation. Our empirical experience was that 10 mg HBB is enough to produce the desired effect on colon spasm with fewer episodes of side effects, i.e. tachycardia. The maximal effect of HBB administered i.v. is reached within 2–8 min and wanes off completely by 30–40 min [5]. As a secondary endpoint, we included polyp detection rate necessitating a second injection at cecum.

HBB administration resulted in less need for external pressure to the abdomen, faster ileal intubation and shorter total procedure time indicating a technically easier procedure. However, VAS ratings between the groups were comparable. Although far from statistical significance, the endoscopist tended to rate colonoscopy slightly easier and less painful in the HBB group. There was also a trend for a shorter cecal intubation time supporting the perception of an easier examination. On the other hand the trend in patients' ratings were opposite.

Due to its anticholinergic activity, HBB has effects on the cardiovascular system [5]. Hence, our finding that HBB induced a significant rise in heart rate and tachycardia during colonoscopy is not new. Yoshikawa et al. [28] reported higher heart rates with 20 mg HBB compared to 1.0 mg glucagon. No difference in the occurrence of tachycardia defined as >100 bpm was observed in their study. Accordingly, Lee et al. [10] reported higher maximum heart rates with patients who received 20 mg HBB as compared to those receiving placebo. Hyoscyamine sulphate 0.5 mg i.v. has provoked tachycardia (>100 bpm) significantly more frequently than placebo (27% vs 3%) [8]. Paralleling this Mui et al. [7] demonstrated higher heart rates and higher incidence of tachycardia (>100 bpm) with 40 mg HBB than with placebo (60% vs 3.6%) concluding that routine administration of HBB is probably not safe, particularly when its benefit remains doubtful. Notably, their dosage of HBB was 40 mg, twice the amount generally used, which may explain the high occurrence of tachycardia. However, although increased heart rate and tachycardia after administration of HBB is frequently observed, no serious adverse events have been reported. This applies also to our study. Unlike previous studies we chose a cut-off 120 bpm instead of 100 bpm for tachycardia because this value might reflect better the true cardiovascular risk provoked by HBB.

We failed to demonstrate any benefit from HBB with regard to polyp detection rate. This is well in line with recent meta-analysis [25–27] although our sample size was probably too small to assess the impact properly. The detection rate in our study (45%) was comparable with previous reports [25–27].

The colonoscopies in the present study were carried out by two experienced endoscopists with the experience of several thousand examinations. Therefore, the results may not necessarily apply to endoscopists with less expertise. Because we wanted to address polyp detection rate we recruited patients aged 45–75 years. Hence, our sample of patients does not completely represent the population we deal with in our daily practice. The potential role of HBB among younger patients remains unclear.

Our randomized, placebo-controlled trial demonstrates that HBB administration decreases the need for external abdominal compression during colonoscopy. It also alleviates ileal intubation and decreases the total procedure time. Otherwise, it seems to be of no significant benefit in terms of technical feasibility or patient tolerance. Although a statistically significant improvement in ileal intubation and total procedure times was achieved with HBB, the clinical significance of these relatively small absolute differences is questionable. HBB administration does not increase polyp detection rate either. HBB induces tachycardia which may be clinically relevant at least in patients with comorbid conditions. Given the fact that HBB provides only a limited improvement in the performance of colonoscopy, routine medication with HBB to facilitate the procedure is probably not justified.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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