

The efficacy of intravenous hyoscine-N-butylbromide during colonoscopy : a prospective, randomized, double-blind, placebo-controlled study

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Abstract

Background and study aims : Colonic spasm makes colonoscopy advancement difficult. This prospective, randomized, double-blind, placebo-controlled study aimed to evaluate the efficacy of hyoscine-N-butylbromide as an antispasmodic during colonoscopy.

Patients and methods : Patients referred for elective colonoscopy were randomized into the study and placebo groups. Before the procedure, the study and placebo groups received 20 mg intravenous hyoscine-N-butylbromide and intravenous saline solution of the same amount, respectively. Demographic and procedure-related data were recorded and compared between the groups.

Results : Of 198 patients referred for elective colonoscopy, 121 were included (study group = 60, placebo group = 61). No differences were observed between the study and placebo groups in terms of demographic data, pre-procedure characteristics, and colonoscopic characteristics including the cecal intubation time, total procedure time, bowel preparation, sedation doses, hemodynamic findings, endoscopist satisfaction, patient comfort, and polyp detection rate. The only difference was an increase in the heart rate by 32% in the study group after hyoscine-N-butylbromide administration ($p < 0.001$).

Conclusions : Hyoscine-N-butylbromide did not reduce the time to reach the cecum and the total colonoscopy time, and patient and endoscopist satisfaction and polyp detection rate did not change. Furthermore, it was concluded that hyoscine-N-butylbromide can increase the risk of drug-related complications. (*Acta gastroenterol. belg.*, 2016, 79, 179-185).

Key words : colonoscopy, premedication, hyoscine-N-butylbromide, colonic polyp.

Introduction

Colonoscopy is the gold standard method to examine colorectal mucosa. Therefore, it is increasingly used in the evaluation of colorectal diseases such as colonic adenoma or cancer, fecal occult blood loss, iron deficiency anemia, inflammatory bowel diseases, colonic tuberculosis, and hematochezia (1,2). Evaluation of the entire area from the anal margin to the cecal pole is important to reduce the rate of missed polyps (3). The folded structure of the intestinal mucosa and the differences in anatomic mobility can make colonoscopy difficult for both the patient and the operator (4). The patient may feel uncomfortable due to distension of the colonic mesentery or distension of the intestinal wall by gas insufflation (5). Loop formation of the colonoscope in the mobile segments of the colon increases this discomfort even further (6). Many operators have tried techniques that can improve patient comfort, shorten the colonoscopy time, and increase the cecal intubation rate (4).

Although many medications have been used for this purpose, the ones that are commonly recognized by endoscopists are antispasmodic drugs (7). Among the anticholinergic antispasmodic medications with good safety profiles, the leading one is hyoscine-N-butylbromide (HBB) (Buscopan ; Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) (4,8). It is extracted from *Duboisia* plant species and was first licensed in the 1950s (4). HBB exerts parasympatholytic activity by blocking muscarinic receptors. This results in decreased motility and tone of the smooth muscle (9). When parenterally administered, it can cause mild and self-limiting side effects such as xerostomia, mydriasis, and tachycardia (10).

Use of antispasmodic agents during colonoscopy is a controversial issue. Colonic spasm can impede advancement of the colonoscope and impair visualization of the mucosal surface, thereby decreasing the detection rate of pathologies that may be cancer precursors such as polyps or adenomas (7). Some studies have reported that intravenous HBB facilitates colonoscopy by relaxation of the colonic smooth muscle (11,12) ; however, other studies contradict this view (7,10,13). Administration of HBB has been suggested to facilitate ileal intubation after reaching the cecum (1) and increase polyp detection rate in patients with moderate to severe colonic spasm (14).

In the present prospective, randomized, double-blind, placebo-controlled study, the effects of HBB administered before colonoscopy on the cecal intubation time, total colonoscopy time, patient and endoscopist satisfaction, and polyp detection rates were investigated.

Patients and Methods

This prospective, randomized, double-blind, placebo-controlled study was conducted between December 2014 and February 2015 at the Surgical Endoscopy Unit of Antalya Training and Research Hospital. The study protocol was approved by the clinical trials ethics committee

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of the hospital (protocol no : 52/11-08.01.2015). Before colonoscopy, signed informed consent was obtained from all participating patients.

Patients

All colonoscopy procedures were performed by 6 specialist endoscopists who had performed over 200 colonoscopies. Patients with an American Society of Anesthesiologists (ASA) score of 1-2 and aged between 18 and 80 years that were referred to the surgical endoscopy unit for elective colonoscopy were included in the study. Patients aged < 18 and > 80 years, those with an ASA score of ≥ 3 , those who had undergone abdominal surgery or colonic polypectomy, those with known allergy to HBB, and those with glaucoma, chronic renal failure, arrhythmia, myasthenia, pregnancy, obstructive uropathy, or autonomic dysfunction were excluded from the study. Patients with inadequate bowel preparation and those in whom cecum intubation could not be performed were also excluded from the study. The demographic, clinical, and colonoscopic characteristics of the patients were recorded.

Randomization and blinding

The patients that were included in the study were assigned by stratified randomization. The patients received either 1 ml of HBB (20 mg) or 1 ml of 0.9% NaCl (saline) intravenously, administered for no longer than 30 s by an anesthesia nurse at the endoscopy room. The endoscopist, independent observer, patient, endoscopy nurse, and room staff were totally blinded to the medication given. The randomization list was accessible only to the anesthesia nurse. From the administration of the medication to the end of the colonoscopy, the pulse oximeter alarm was put on silent mode and turned to a direction where it could not be seen by the endoscopy team. In this way, the tachycardia effect that can be seen with HBB was masked. However, for patient safety, the endoscopist was informed in case of serious tachycardia (heart rate of > 140 beats per min).

Study procedure

All patients were given low-fiber diet for 3 days before the procedure. Two doses of laxatives containing 250 cc sennoside A and B or 45 cc phospho soda were given the day before the procedure. In addition, for distal colonic irrigation, 2 doses of enema liquids containing disodium phosphate and sodium phosphate or sodium dihydrogen phosphate and disodium hydrogen phosphate were given. All procedures were performed using video colonoscopes (Fujinon VP-4450 HD and Fujinon EPX-2500, Fujifilm Co., Tokyo, Japan).

Oxygen saturation and heart rate were monitored for all patients. Following examination of key hemodynamic profiles, the patients were repositioned to the left lateral position. Oxygen at 3 L/min using a face mask was initi-

ated for support. Before the procedure, 1 mg/kg of propofol or 0.05 mg/kg of midazolam for sedation and 1 μ g/kg of fentanyl for analgesia were administered intravenously. No additional sedation or analgesia was performed during the procedure. The study group received HBB, whereas the placebo group received 0.9% NaCl (saline). Vital signs, including heart rate and peripheral blood saturation, were monitored throughout the procedure; pre- and post-medication values were recorded.

For each procedure, the cecal intubation time was recorded. This was defined as the interval between insertion of the colonoscope into the anus and reaching the cecal pole. The position of the cecal pole was identified by confirmation of the appendiceal orifice and ileocecal valve by an independent assessor. The total procedure time was defined as the time between insertion of the colonoscope into the anus and its removal from the anus. Bowel cleanliness was evaluated using Boston Bowel Preparation Scale (BBPS) (15), which scores colon cleanliness from 0 (unprepared) to 3 (clean). Because unprepared patients were excluded from the study, BBPS scores were between 1 and 3 points. Immediately after the procedure, the endoscopist rated technical difficulty of the colonoscopy and patient's cooperation; patient satisfaction was based on the severity of pain: 1 = very bad, 2 = bad, 3 = good, 4 = very good. (16). In addition, presence or absence of polyps was recorded regardless of location, type, and size. Considering the fact that the hepatic flexure is one of the most challenging anatomic locations to be passed through using various manipulations during colonoscopy and that it can affect the colonoscopy time, passage from the hepatic flexure was recorded as easy or difficult. After complete recovery, the independent assessor evaluated satisfaction of the patients using the visual analog scale (VAS) (0-10).

Statistical Methods

Statistical analysis was performed using SPSS for Windows 21.0 software. Demographic and clinical characteristics of the patients were expressed using mean \pm standard deviation (SD), median, range, and percentage (%) values. The study and placebo groups were compared. Parametric data were analyzed using Student's *t* test and repeated-measure analysis of variance, whereas non-parametric data were analyzed using the Mann-Whitney U, χ^2 , and Friedman tests. Association between numeric data was evaluated using correlation analysis. The results were evaluated to be significant at a *p* level of <0.05 within 95% confidence interval (CI).

Results

In total, 198 patients were referred to our unit for elective colonoscopy between December 2014 and February 2015. Of these, 17 patients that met ≥ 1 exclusion criteria and 32 patients with inadequate bowel preparation (BBPS score of 0) were excluded from the

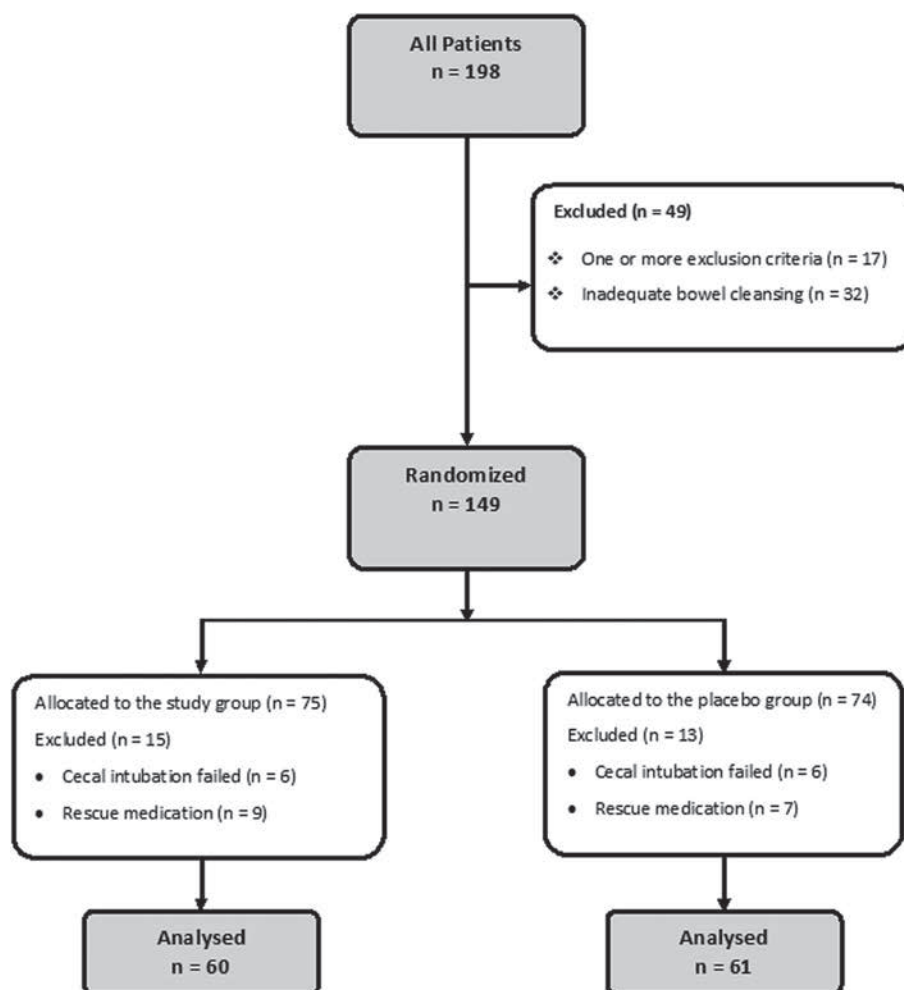


Fig. 1. — Flow chart of the trial

study. Of 149 patients who were randomized, 12 were excluded because of failed cecal intubation due to obstruction or patient intolerance and 16 were excluded because of requirement for additional sedation or analgesia. In total, 121 patients (60 in the study group and 61 in the placebo group) were analyzed (Fig. 1). The patients' characteristics are summarized in Table 1. These included age, gender, weight, height, body mass index (BMI), previous history of colonoscopy, ASA score, and colonoscopy indications. The indications were classified into main categories: diarrhea and chronic constipation; change in bowel habit, and any type of rectal bleeding. Rare symptoms such as tenesmus, rectal pain, anemia, and abdominal distension were classified as others. The colonoscopic characteristics such as the cecal intubation time, total procedure time, bowel preparation, sedation doses, haemodynamic findings, endoscopist satisfaction, patient comfort or polyp detection rate are presented in Table 2. According to these results, the study group did not differ from the placebo group in terms of the cecal intubation time, total procedure time, patient and endoscopist satisfaction, polyp detection rate, and diagnoses. The only difference

between the groups was tachycardia after administration of HBB, which significantly increased the heart rate by 32% in the study group ($p < 0.001$). None of the patients required additional intervention or discontinuation of the procedure due to tachycardia.

Overall, the cecal intubation time and total procedure time were not affected by age, height, body weight, BMI, sedation doses, pre-procedure indications, and bowel cleanliness but were significantly affected by gender, presence of polyps, level of difficulty in passage from the hepatic flexure, and post-procedure diagnoses (Table 3); in the placebo group alone, male gender was not contributory. Difficulty of passage from the hepatic flexure did not affect the total procedure time in the study group but prolonged all the other time-related procedural measurements. Presence of polyps increased the total procedure time in both groups but did not change the cecal intubation time. In diagnostic terms, procedural times were prolonged due to biopsy procedures and with increasing severity of colonoscopy findings from normal to colonic polyps and colon cancers.

No procedure-related mortality or morbidity was seen in any of the patients.

Table 1. — Characteristics of the study and placebo groups

	Study Group (n = 60)	Placebo Group (n = 61)	p
Age (years) ^a	52 ± 15 (18-79)	55 ± 14 (19-76)	0.098
Gender (male/female)	31/29	34/27	0.347
Height (cm) ^a	165 ± 8	164 ± 9	0.935
Weight (kg) ^a	74 ± 16	76 ± 11	0.834
BMI (kg/m ²) ^a	27 ± 5	28 ± 5	0.645
Patients with previous colonoscopy	4 (6%)	5 (8%)	0.244
ASA I/II	26/34	25/36	0.182
Indications for colonoscopy			0.293
Screening or FOBT positive	23 (38%)	26 (43%)	
Abdominal pain	10 (16%)	8 (13%)	
Rectal bleeding	13 (22%)	11 (18%)	
Change in bowel habit (%)	3 (5%)	4 (6%)	
Others (%)	11 (19%)	12 (20%)	

BMI, *body mass index* ; ASA, American Society of Anesthesiologists ; FOBT, fecal occult blood test.

^aMean ± standard deviation.

Discussion

Colonoscopy is the preferred method in most patients with colonic diseases (17). Therefore, it is important to evaluate all areas of the colon (3). However, colonoscopy may not be the ideal procedure for all cases. Many studies have reported that polyps and cancers may be overlooked due to incomplete bowel cleanliness, colonoscopic technique, polyp location, and colonic contractility (11,12,18-21). Colonic spasm can make the procedure difficult for endoscopists in terms of visualization of the mucosa and advancement of the colonoscope (22). Adequate colonic distension for good mucosal visualization can also increase detection rates of overlooked polyps and adenomas (23,24). Many pharmacological agents have been tried for this purpose. The best known drugs are dicyclomine hydrochloride (22,25), glucagon (23,26), and atropine (27,28), which did not show any benefits.

Another agent preferred for antispasmodic effects is HBB, which has been commonly preferred for its physiopathological effects as well as its low cost and broad safety profile (29). It has been routinely used by radiologists to facilitate mucosal exploration and to decrease colonic motility during CT colonoscopy and barium enema investigations (8,30). HBB has also been frequently preferred by gastroenterologists. A survey conducted in the UK showed that HBB is administered with a frequency of 20%-50% to facilitate cecal intubation and to accelerate the procedure (31). Saunders and Willams (11) found that colonic spasm is less frequently seen and the cecal intubation time is shorter in patients who received HBB. Similarly, other studies have reported a shorter sigmoidoscopy procedure time (12,22). Misra *et al.* (1) and Ansari *et al.* (32) demonstrated that ileal intubation is facilitated by HBB. On the contrary, Shaheen *et al.* (33)

and Dumot *et al.* (34) reported that HBB is not beneficial, and Mui *et al.* (7) found that HBB increases the cecal intubation time. Similarly, the present study found that HBB did not exert favorable effects on the cecal intubation time.

Some studies have used the withdrawal time, whereas others have used the total procedure time as parameters to evaluate the efficacy of colonoscopy. However, it is possible that neither of these is a good indicator of clinical outcomes because they can be affected by factors such as the time utilized for the removal of polyps or for passage through deep folds (35). Conflicting publications reported that HBB decreases (36), increases (37), or does not change these times (10,13,29,38). In the present study, there were no differences in terms of the total procedure time between both groups. However, the total procedure time was prolonged in males, in whom passage from the hepatic flexure is difficult, and in patients in whom polyps and cancers were detected. The most important factor was the fact that polypectomy or biopsy was performed during withdrawal.

The effects of HBB on polyp detection have been investigated in many studies. It is hypothesized that HBB facilitates the detection of small and flat polyps by removing deep folds. Many studies support this theory (21,37). In these studies, HBB was administered after cecal intubation, thereby homogenizing the possibility of polyp detection. In a study conducted in 2001, Tee *et al.* (39) compared cap-assisted colonoscopy versus standard colonoscopy. They reported increased polyp detection rate in patients who received HBB. However, there are studies that assert the contrary (10,14,29,37,40). Cui *et al.* (41) and Rondonotti *et al.* (35), who evaluated these studies in their meta-analyses, concluded that probably, HBB is not effective in the detection of polyps or

Table 2. — Colonoscopic characteristics and hemodynamic results of the study and placebo groups

	Study Group (n = 60)	Placebo Group (n = 61)	p
Cecal intubation time (min) ^a	10 ± 3	11 ± 4	0.306
Total procedure time (min) ^a	15.6 ± 4	14.6 ± 5	0.415
Bowel preparation			0.768
Excellent	28 (47%)	28 (46%)	
Good	29 (49%)	27 (44%)	
Poor	3 (4%)	6 (10%)	
Sedation and analgesic doses ^a			
Propofol dose (mg)	68.4 ± 30	65.1 ± 31	0.092
Midazolam dose (mg)	2.3 ± 0.6	2.1 ± 0.9	0.276
Fentanyl dose (µg)	90.4 ± 27	86.4 ± 35	0.186
Hemodynamic status ^a			
Heart rate before medication (beats/min)	76 ± 15	82 ± 12	0.109
Heart rate after medication (beats/min)	100 ± 17	81 ± 12	< 0.001
SpO ₂ before medication (%)	98 ± 1	96 ± 3	0.127
SpO ₂ after medication (%)	98 ± 1	98 ± 2	0.545
Presence of polyps			0.251
Yes	17 (46%)	18 (45%)	
No	43 (54%)	43 (55%)	
Passage from the hepatic flexure			0.194
Easy	33 (55%)	21 (35%)	
Difficult	27 (45%)	40 (65%)	
Endoscopist satisfaction score			0.830
Very bad	5 (8%)	10 (18%)	
Bad	27 (45%)	18 (29%)	
Good	12 (20%)	18 (29%)	
Very good	16 (27%)	15 (24%)	
VAS score ^a	2.9 ± 2	3 ± 1	0.944
Diagnoses			0.758
Normal colonoscopy	32 (54%)	33 (55%)	
Colon polyps	17 (28%)	18 (29%)	
Colon cancer	5 (8%)	2 (3%)	
Colon diverticulum	3 (5%)	6 (10%)	
Inflammatory colitis	3 (5%)	2 (3%)	

SpO₂, Saturation of peripheral oxygen; VAS, Visual analog scale.

^aMean ± standard deviation.

adenomas. Similar to these findings, the present study also found no differences between the study and placebo groups in terms of polyp detection rates. Because the primary objective of the study was to evaluate the cecal intubation time and total procedure time, HBB was administered before the procedure.

Another objective of the study was to evaluate patient and endoscopist satisfaction. In their study on 150 patients, Dumot *et al.* (34) found that sublingual hyoscine decreased post-procedure pain. The study by Kayaoğlu *et al.* (27) found significantly lower post-

procedure VAS scores in the HBB group ; no pre-medication was administered for sedation in this study. On the contrary, a randomized, double-blind, placebo-controlled study showed that neither oral nor intravenous hyoscine had an effect (33). Similarly, another study on 675 cases did not find any difference between the groups in terms of the VAS score (29). In a patient-controlled sedation, Mui *et al.* (7) reported no difference in the VAS score and endoscopist satisfaction was lower in the HBB group. Sulu *et al.* (36) administered sedation before the procedure and found no difference between the HBB

Table 3. — Factors affecting cecal intubation time and total procedure time

	Study Group (n = 60)		Placebo Group (n = 61)		Both Groups (n = 121)	
	Cecum	Total	Cecum	Total	Cecum	Total
Male gender	NS	0.004	NS	NS	NS	0.008
Passage from the hepatic flexure	0.004	NS	0.001	0.002	0.001	0.004
Presence of polyps	NS	0.04	NS	0.03	NS	0.002
Diagnoses	NS	0.006	0.03	0.01	0.04	0.001

NS, Not significant.

Spearman correlation analysis was used.

group and the control group in terms of the VAS score and endoscopist satisfaction. The results of our study are compatible with these reported findings.

HBB is a well-tolerated and safe medicine. Its most common side effects are visual accommodation disturbance, mild tachycardia, and dry mouth. Urinary retention, nausea, and mild hypertension are rarely seen and dyshidrosis, flushing, and dizziness are uncommon (8,24). Any medication administered parenterally during procedure has potential side effects such as allergic reactions that may result in anaphylaxis. Although extremely rare, anaphylaxis after intramuscular administration of HBB was reported in literature in only 1 patient (42). Tachycardia is the most commonly reported side effect of HBB (7,22,38,40). In this study seen the similar side effects with the use of HBB. This suggests a question on whether a pharmacologic agent with disputable benefits for colonoscopy can be routinely used. Moreover, the fact that most colonoscopy patients are treated as outpatients and that most of them are elderly and therefore may have co-morbid conditions poses a danger in terms of possible side effects (7). Similarly in our study, the tachycardia effect of HBB was observed, but the heart rate of patients did not increase to levels that required discontinuation of the procedure or additional treatment.

The study had several limitations. First is the single-center design. Moreover, performance of the procedures by 6 experienced endoscopists may have caused heterogeneity in terms of their techniques. The second limitation is that the number, size, and location of the polyps could not be recorded. Because the primary study variables were procedure times and patient and endoscopist satisfaction, only the presence of polyps was recorded. The third limitation is that more intense sedation and analgesia were administered in the present study than in previous studies. This may have affected post-procedure pain scores. In addition, because of the short-term amnesia effect of midazolam, perceptual change may have occurred in patients after the procedure; therefore, they may have given different answers to questions asked. Finally, parameters such as patient and endoscopist satisfaction and passage from the hepatic flexure are subjective and despite the presence of an independent assessor,

these parameters may have varied depending on the person performing the procedure.

In conclusion, use of an antispasmodic agent had no favorable effects on the time to reach the cecum, total colonoscopy time, patient and endoscopist satisfaction, and polyp detection rates. Moreover, the risk of drug-related complications, particularly tachycardia, can increase.

Declaration of interest

The authors report no financial relationships or conflicts of interest regarding the content here in.

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