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Original article

The effect of premedication with peppermint oil capsules (Colpermin) prior to colonoscopy: A double blind randomized placebo-controlled trial

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ABSTRACT

Background and study aims: Colonoscopy is the cornerstone of diagnosing colonic diseases. Investigators have evaluated the effectiveness of antispasmodic agents in colonoscopy with conflicting evidence. The aim of this study is to determine the efficacy of enteric coated peppermint oil capsules (Colpermin®), an antispasmodic agent, on outcomes during colonoscopy.

Patients and methods: A total of 80 patients undergoing elective colonoscopy were recruited and randomized in a double blinded fashion to receive either placebo or peppermint oil capsules administered 4 h prior to the procedure.

Results: Peppermint oil capsules did not affect caecal intubation time when compared with placebo. Patients' tolerance, endoscopist's satisfaction and demand on sedation were also not affected.

Conclusion: This randomized controlled trial does not support the routine use of peppermint oil capsules prior to colonoscopy as a tool for procedure optimization, and patients' and endoscopist's satisfaction.

Introduction

Colonoscopy is an integral component in the diagnosis and treatment of colorectal diseases. It is a widely performed procedure nowadays and is being increasingly demanded worldwide [1]. It has been shown advantageous in the long-term prevention of colorectal cancer (CRC) through the detection and removal of precancerous adenomas [2,3]. Screening colonoscopy of potentially at risk patients has been recommended by many expert panels including the American College of Gastroenterology [4].

Colonoscopy has two components in terms of time, caecal intubation time and withdrawal time; this excludes intervention time [5]. Caecal intubation time is defined as the duration required from anal insertion of the colonoscope until reaching the tip of the cecum. It is often used as a measure of procedural complexity [5,6]. Complex colonoscopies are frequently associated with painful and unbearable experience by patients. Multiple elements have been identified as risk factors for difficult colonoscopy. These are either operator dependent, such as the overall skill of the endoscopist, or patient dependent such as anatomic variation, poor bowel preparation, adhesions from prior surgery or a spastic colon [7,8].

It is essentially important for colonoscopy to be carried out with the highest possible standards. Caecal intubation time is one of the most commonly used quality indicators [1,9]. Caecal intubation varies greatly between patients as it depends upon the complexity of the case. This measure is important for several reasons. It is proportionally related to patients' experience of pain, sedation requirements and sedation related complications [10].

The aim of this randomized placebo-controlled prospective trial, is to investigated the impact of peppermint oil (Colpermin®, Tillotts Pharma, Ziefen, Switzerland), an antispasmodic agent, on caecal intubation time, patients' tolerance, endoscopist's satisfaction as well as demand for sedation.

Patients and methods

This trial was conducted at Al-Zahraa Hospital, a major teaching hospital affiliated to the Lebanese University, Beirut, Lebanon.

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A total of 80 patients with indications for colonoscopy (Table 1) were enrolled. The trial was conducted between January 2015 and January 2016. It was approved by the ethical committee at the Lebanese University and is in accordance with the Helsinki Declaration. The inclusion criteria included patients with ages between 25 and 85, ability to complete a post-colonoscopy questionnaire, and not on any antispasmodic medication. Patients with multiple comorbidities e.g. severe cardiac or pulmonary disease, history of colonic resection or multiple abdominal surgeries, substance abuse, glaucoma, history of allergy to peppermint oil, as well as pregnant or lactating women were excluded.

Prior to enrollment, all patients enrolled signed an informed consent and completed the study subsequently. Patients were randomized into two arms in a 1:1 manner; either to receive placebo comprised of vitamin B12 or Colpermin® (Tillotts Pharma, Ziefen, Switzerland). The Colpermin dosage used was 374 mg (2 enteric coated capsules of 187 mg dose each). Randomization was done by means of opening a sealed envelope. The envelopes had been sealed by an independent person who is not attending the trial in any other way. Both patients and investigators were blinded to the treatment given. A standard bowel preparation was done using 4 l of polyethylene glycol one day prior to the procedure (Moviprep, Norgine Limited, Hengoed, Great Britain). The medication was administered about 4 h prior to the insertion of the colonoscope, where peak release of Colpermin in the colon occurs [11]. All colonoscopies were performed by one experienced endoscopist (A.L) using standard Olympus GIF 2TH180 colonoscope (Olympus Optical Co., Ltd., Tokyo, Japan). No additional colonoscope features were used. Air insufflation only was used. Biopsies and polypectomies with standard techniques were done only if indicated. Sedation was given in a stepwise progressive dose on patients' demand using midazolam and meperidine.

Patients' baseline characteristics were collected and are presented in Table 1. The primary endpoint of the trial was to measure the caecal intubation time. Secondary endpoints were subjective and included: degree of colonic spasm assessed by the endoscopist (no movement, minimal, mild, moderate or marked), endoscopist's satisfaction score (easy, fairly easy, difficult, or failure to complete), patients' discomfort (no pain, mild, moderate, or severe), willingness to repeat colonoscopy (yes or no) and demand for sedation (meperidine and midazolam dosage).

All data were analyzed using SAS version 9.3. Quantitative variables were presented as mean ± SD. Independent sample *t*-test was used to compare normally distributed continuous variables in different groups. Categorical outcome variables were analyzed via Chi-square or Fisher's exact tests. The Cochran–Armitage test for trend was used in categorical data analysis when the aim was to assess for the presence of an association between a variable with two categories and a variable with *k* categories. This test modifies the Pearson chi-squared test to incorporate a suspected ordering in the effects of the *k* categories of the second variable. A p-value less than 0.05 was considered statistically significant.

Results

The trial was 80% powered to detect approximately 1.5 mins difference between placebo and Colpermin. A total of 80 patients were randomized. Of them, 39 patients received Colpermin 374 mg and 39 patients received placebo. Two patients were excluded from the analysis; one of them had inadequate bowel preparation, and the other failed to show up. The demographic data of trial participants is presented in Table 1. There were no significant disparities between both groups in terms of age, sex, smoking status, indication of colonoscopy, final diagnosis following colonoscopy and quality of bowel preparation. Outcome measures representing primary and secondary endpoints are presented in Table 2. Statistical analysis didn't show any difference in time to caecal intubation as the primary endpoint (p = .4). In addition, there was no statistical significance in secondary endpoints characterized by colonic spasm score, (p = .9), endoscopist's satisfaction score (p = .8) pain score assessed by the patient (p = .9), willingness

Table 1
Patients characteristics.

	Total (n = 78)	Placebo (n = 39)	Colpermin (n = 39)	P-value
Age (Years)				
Mean ± SD	50.6 ± 13.9	50.8 ± 11.7	50.4 ± 16.0	0.9†
Range	25–83	26–70	25–83	
Sex (M:F)	36/42	18/21	18/21	1.0‡
Smokers (%)	47 (60)	20 (51)	27 (69)	0.1‡
No. of patients with previous colonoscopy (%)	20(26)	12 (31)	8 (21)	0.3‡
Indication for colonoscopy				
Diarrhoea (%)	21 (27)	12 (31)	9 (23)	0.4‡
Bloody diarrhoea (%)	6 (8)	5 (13)	1 (3)	0.1*
Iron deficiency anaemia (%)	16 (21)	9 (23)	7 (18)	0.6‡
Abdominal pain (%)	28 (36)	10 (26)	18 (46)	0.1‡
Rectorrhagia (%)	9 (12)	4 (10)	5 (13)	0.3‡
Others (%)	8 (10)	7 (18)	1 (3)	
Diagnosis				
Normal (%)	17 (22)	8 (21)	9 (23)	0.8‡
IBS (%)	13 (17)	6 (15)	7 (18)	0.8‡
Mass (%)	4 (5)	2 (5)	2 (5)	1.0*
CD (%)	10 (13)	6 (15)	4 (10)	0.5‡
UC (%)	5 (6)	1(3)	4 (10)	0.4*
Others (%)	29 (37)	16 (41)	13 (33)	
Quality of bowel preparation				0.8§
Excellent (%)	0 (0)	0 (0)	0 (0)	
Good (%)	41 (53)	20 (51)	21 (54)	
Fair (%)	26 (33)	15 (38)	11 (28)	
Inadequate (%)	11 (14)	4 (10)	7 (18)	

Abbreviations: CD: Crohn's Disease; IBS: Irritable Bowel Syndrome; No: Number; SD: standard deviation; UC: Ulcerative Colitis.
† Independent samples *t* test.
‡ Chi-square test.
* Fisher's exact test.
§ Cochran–Armitage test.

to repeat colonoscopy (p = .9) and demand for sedation (midazolam, p = .3; meperidine, p = .6). No adverse events were recorded in both arms.

Discussion

Colonoscopy is considered an invasive procedure with multiple technicalities. The procedure can sometimes be impeded by colonic spasm. This might increase the total time of the procedure leading to increased doses of sedation. In addition, colonic spasms can limit colonic pathology assessment and increase patients' discomfort. The pain encountered during the procedure is a consequence of gas insufflation, which places tension by stretching on the mesenteric attachments [12,13].

Antispasmodic medications have been used for many years as a premedication prior to colonoscopy. Their use was justified by their pharmacological properties as they induce intestinal smooth muscle relaxation and flattening of the haustral folds. All these effects proposed the hypothesis of attaining a better colonoscopy by easing scope advancement, improving mucosal visualization and adenoma detection, and reducing caecal intubation time [3]. However, controversy still exists regarding their clinical benefit, and several randomized controlled trials were done evaluating antispasmodics role in colonoscopy. The most frequent drug used was hyoscine N-butylbromide (HBB). Two recent meta-analyses failed to show any benefit from HBB use during colonoscopy in terms of polyp and adenoma detection [14,15].

Peppermint oil, a well-known herb that has been used for many years for its significant therapeutic and antispasmodic efficacies in IBS patients [16]. It has been shown beneficial in reducing gastric spasm during upper endoscopy and was useful during ERCP by inducing duodenal relaxation [17,18]. It was also shown advantageous in improving diagnostic quality of double-contrast barium meal examination [19]. The main component of peppermint oil extract is menthol, a chemical compound well recognized for its relaxant effect on intestinal smooth muscles and modulation of visceral hypersensitivity [16,20,21]. This effect of reduced mechanical colonic activity is induced mainly by blocking Ca^{2+} influx through sarcolemma voltage-dependent L-type Ca^{2+} channels [22]. The characteristics of peppermint oil made it an attractive choice for use. The advantages of its administration over other anticholinergic agents include a relatively rapid onset of action, and its oral route administration, in comparison to systemic administration of other agents such as HBB [11,12,14].

To our knowledge, two randomized controlled trials have evaluated the effect of peppermint oil during colonoscopy [23,24]. Shavakhi et al. (2012) who recruited a total of 66 patients divided into two groups (placebo and colpermin) and demonstrated a statistically significant reduction in time needed to complete colonoscopy, time needed for caecal intubation and colonic spasm score. Asao et al. (2001), on the other hand, used intraluminal peppermint oil during colonoscopy, which demonstrated a significant reduction in the grade of spasm, but no observed difference in mean time for caecal intubation.

In this study, we failed to demonstrate any benefit from Colpermin in terms of caecal intubation time, endoscopist's satisfaction, patients' discomfort, colonic spasm score and demand for sedation. While conducting the study, every effort was made to minimize bias. Patients were matched for possible confounding factors including age, sex, and indication of colonoscopy. Because it is well known that colonoscopy outcomes are significantly affected by endoscopist skills, all the procedures were performed by one endoscopist aiming for more accurate results. Consequently, the fact that this study was done by one physician and was negative suggests a true lack of clinically significant benefit from colpermin. On the other hand, it is important to mention that both placebo and colpermin tablets are not visible in the colon, which further add another point of strength to the study by eliminating investigator bias.

However, this study should be interpreted in context of its limitations. First, the sample size was only powered to detect a 1.5 mins difference in caecal intubation time. Second, the effects of sedatives and analgesics perhaps served as possible confounding factors that could have diminished or masked the true effect of Colpermin on the procedure [25]. Third, short term anterograde amnesia resulting from midazolam administration might have subjectively influenced the patients' questionnaire [26]. Fourth,

Table 2
Outcome measures after colonoscopy.

	Total (n = 78)	Placebo (n = 39)	Colpermin (n = 39)	P-value
Cecal intubation time (min)				
Mean ± SD	7.8 ± 3.4	7.5 ± 2.6	8.1 ± 4.0	0.4†
Range	3–20	3–12	3–20	
Colonic spasm score				0.9§
No movement (%)	19 (24%)	9 (23%)	10 (26%)	
Minimal (%)	9 (12%)	6 (15%)	3 (8%)	
Mild (%)	15 (19%)	8 (21%)	7 (18%)	
Moderate (%)	19 (24%)	5 (13%)	14 (36%)	
Marked (%)	16 (21%)	11 (28%)	5 (13%)	
Pain score				0.9§
No pain (%)	19 (24%)	11 (28%)	8 (21%)	
Mild (%)	24 (31%)	11 (28%)	13 (33%)	
Moderate (%)	20 (36%)	7 (18%)	13 (33%)	
Severe (%)	15 (19%)	10 (26%)	5 (13%)	
Endoscopic satisfaction score				0.8§
Easy (%)	24 (31%)	12 (31%)	12 (31%)	
Fairly easy (%)	28 (36%)	14 (36%)	14 (36%)	
Difficult (%)	18 (23%)	8 (21%)	10 (26%)	
Failure to complete (%)	8 (10%)	5 (13%)	3 (8%)	
No. of patients willing to repeat colonoscopy (%)	51 (65%)	25 (64%)	26 (67%)	0.9‡
Demand on sedation				
Midazolam (Mean ± SD)		5.0 ± 0.89	4.7 ± 0.88	0.3†
Merperidine (Mean ± SD)		46 ± 9.2	45 ± 11.7	0.6†

Abbreviations: SD: standard deviation; No: Number.
† Independent samples *t* test.
‡ Chi-square test.
§ Cochran–Armitage test.

the quality of bowel preparation was suboptimal which can also be a confounding factor, as poorer bowel preparation has been associated with longer caecal intubation time [27]. In our study, due to the difficulty in examining the effect of premedication with peppermint oil in the setting of split dosage preparation we preferred to use full dose colonic preparation though it is well known to be inferior, and this could be a sufficient explanation for the suboptimal quality of bowel preparation our patients had. Finally, though the placebo was not perfectly matched, a huge effort was done to prevent a breach of double blindness and this was confirmed by the negative result of the study which signify lack of potential unblinding.

In conclusion, the present study shows no benefit for the routine use of peppermint oil capsules prior to colonoscopy to as a means of procedural optimization.

Conflict of interest

The authors have no conflict of interest

Compliance with ethical standards

The submitted manuscript involves research done on humans and has been approved by the ethics committee of the Lebanese University. Informed consents were signed by all enrolled patients.

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