

[ORIGINAL ARTICLE]

A Prospective Study of Factors Associated with Abdominal Pain in Patients during Unsedated Colonoscopy Using a Magnifying Endoscope

Hiroto Suzuki¹, Masanao Nakamura¹, Takeshi Yamamura², Keiko Maeda², Tsunaki Sawada², Yasuyuki Mizutani¹, Takuya Ishikawa¹, Kazuhiro Furukawa¹, Eizaburo Ohno¹, Takashi Honda¹, Hiroki Kawashima¹, Masatoshi Ishigami¹ and Mitsuhiro Fujishiro¹

Abstract:

Objective With the advent of endoscopic treatment, the detailed diagnosis of colorectal neoplasms made using magnifying colonoscopy has become increasingly important. However, insertion difficulty causes pain in unsedated colonoscopy. The aim of this prospective observational study was to clarify the factors associated with a patient's pain in unsedated colonoscopy using a magnifying endoscope.

Methods Patient pain was assessed using a numerical rating scale (0-10) immediately after the procedure. We defined 5 as mild enough pain that patients would not be reluctant to undergo another colonoscopy. Acceptable pain was defined as 5 or less and severe pain was defined as 8 to 10. Univariate and multivariate linear regression analyses were performed using the pain scale score as a dependent variable.

Results A total of consecutive 600 patients undergoing unsedated colonoscopies were evaluated to assess their abdominal pain. The completion rate was 99.5% (597/600). The mean pain scale score was 3.88 ± 2.38 . The rate of acceptable pain was 80.5% (483/600). The rate of severe pain was 6.7% (40/600) including the incomplete cases. A comparison of polyp-positive and polyp-negative cases revealed no marked difference in patient pain (3.82 ± 2.24 vs. 3.94 ± 2.49 , respectively; $p=0.590$) or insertion time (6.62 ± 3.98 vs. 6.29 ± 4.21 , $p=0.090$), while more observation time was needed in polyp-positive cases than in polyp-negative ones (16.30 ± 4.95 vs. 13.08 ± 4.69 , $p<0.01$). Univariate and multivariate linear regression analyses revealed that an older age, colectomy, antispasmodic agent use, and a small-diameter endoscope were significant factors associated with less patient pain. In particular, a small-diameter endoscope induces significantly more acceptable pain than a non-small diameter endoscope [85.63% (274/320) vs. 73.93% (207/280), $p=0.00003$].

Conclusion Unsedated colonoscopy using a magnifying endoscope by an expert may result in acceptable pain levels. The use of an antispasmodic agent, particularly hyoscine N-butyl bromide, and a small-diameter endoscope are recommended for reducing abdominal pain during unsedated colonoscopy.

Key words: unsedated colonoscopy, magnifying endoscope, pain, antispasmodic agent

(Intern Med 59: 1795-1801, 2020)

(DOI: 10.2169/internalmedicine.4267-19)

Introduction

The incidence of colorectal cancer is increasing worldwide. Accordingly, colonoscopy has become increasingly

important because it enables a reduction in mortality rates and incidence via adenoma removal (1, 2); intramucosal carcinoma and shallow invasive submucosal carcinoma (sSM: T1a; $<1,000 \mu\text{m}$) can be treated endoscopically (3, 4).

Endoscopic submucosal dissection (ESD) and cold

¹Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Japan and ²Department of Endoscopy, Nagoya University Hospital, Japan

Received for publication November 27, 2019; Accepted for publication March 8, 2020

Correspondence to Dr. Masanao Nakamura, makamura@med.nagoya-u.ac.jp

polypectomy (CP) were recently and widely introduced as new standard endoscopic treatments for colorectal lesions. Large superficial lesions that were previously difficult to treat can now be resected en bloc endoscopically by ESD (5, 6). CP saves time in the resection of small (<10 mm) adenoma. The risk of post-polypectomy bleeding by CP was reportedly the same as that of bleeding with hot-snare polypectomy (7, 8). However, larger lesions were more likely to be deep invasive carcinoma (dSM: T1b; $\geq 1,000 \mu\text{m}$), which carries a risk of lymph node metastasis, whereas small lesions are infrequently carcinoma. Cases of dSM should not be treated endoscopically, even by ESD, while small lesions containing carcinoma should be resected with sufficient margins via endoscopic mucosal resection (EMR) due to their risk of recurrence. Therefore, it is important to reach a detailed and accurate endoscopic diagnosis before treatment.

The pit pattern diagnostic system is among the most reliable methods for diagnosing colorectal lesions (9, 10), but it requires time for the spraying of crystal violet. Therefore, a new diagnostic system, The Japan NBI expert team (JNET) classification, based on magnifying endoscopy, was proposed in 2016 (11). The JNET classification can differentiate between intramucosal cancer and sSM. In the JNET classification, colorectal lesions are classified into four categories based on the micro-vessel pattern and micro-surface features on image-enhanced magnifying endoscopy: Type 1 indicates hyperplastic polyps that did not require resection; Type 2A indicates adenoma requiring resection; and Type 3 indicates dSM that cannot be treated endoscopically. In addition, because Type 2B includes adenoma, intramucosal carcinoma, sSM, and dSM, it should be additionally diagnosed by the pit pattern diagnostic system (11, 12).

We are currently required to select the endoscopic treatment strategy [CP, Hot polypectomy (HP), EMR, or ESD] based on the detailed endoscopic diagnosis made via magnifying endoscopy. However, a magnifying colonoscope is not generally used because it is difficult to insert, more time is required for a diagnosis made using a magnifying colonoscope, and it tends to cause more pain.

One of the most effective methods for reducing patient abdominal pain is sedated colonoscopy. Some studies have shown that sedated colonoscopy features a high completion rate and low rate of pain (13, 14). However, the use of sedation is unreasonable for every patient because sedated colonoscopy carries risks of adverse events (e.g., cardiovascular events, perforation) and is associated with higher costs and a longer examination time (15-18). Furthermore, patients who were examined under sedation reportedly experienced more discomfort than those without sedation (19). Using non-magnifying endoscopes, unsedated colonoscopy was found to be acceptable for some patients (20, 21). Being able to determine whether or not patients should receive sedation before the procedure will contribute to clinical practice. Previous studies have shown that factors associated with painful colonoscopy include age (13, 22, 23),

sex (13, 22-24), body mass index (BMI) (23), bowel preparation (22, 23, 25), history of abdominal surgery (24), history of hysterectomy (22, 23, 25), endoscopists' experience (24, 25), diverticulum (26), antispasmodic agent use (14, 22, 27), carbon dioxide (CO₂) (28, 29), and endoscope diameter (13, 30). However, these factors were revealed by studies using non-magnifying endoscopes, and the insertability of the magnifying endoscope and patient pain induced by its use have not been clarified.

Recently, several novel magnifying endoscopes with variable stiffness and smaller diameters than previous magnifying endoscopes have been developed. These features may improve the endoscope insertability and patient pain. We usually perform unsedated colonoscopy using a magnifying endoscope at our hospital. However, we have never examined patient acceptability or factors associated with induced pain. Colonoscopy using a magnifying endoscope is required to determine the indication for endoscopic treatment. It is important to consider whether or not the procedure can be performed without sedation. The aim of this study was to prospectively clarify the factors associated with patient pain during unsedated colonoscopy using a magnifying endoscope.

Materials and Methods

This single-center prospective observational study was approved by the ethics committee of Nagoya University Hospital. This study was registered at the University Hospital Medical Information Network in the Clinical Trials Registry (UMIN000024026).

Patients

Patients ≥ 20 years old who were able to give their informed consent and scheduled for unsedated colonoscopy at Nagoya University Hospital, academic hospital, between June 2016 and November 2017 were enrolled. Patients were recruited in daily clinical practice, not at an annual medical screening examination. Patients who hoped to be sedated, those who were scheduled to undergo a detailed examination of colorectal tumors that had already been diagnosed, and those with active bleeding, severe inflammation, severe comorbidities, polyposis, or dementia were excluded. We defined indications into three categories: surveillance, diagnosis without symptoms (positive fecal occult blood test, and malignant tumor detected in other organs), and diagnosis with symptoms (abdominal pain, bloody stool, constipation, diarrhea).

Endoscopy methods

All colonoscopies were performed by experienced endoscopists who had performed at least 2,000 colonoscopies. Patients were administered 1-2 L of polyethylene glycol (Moviprep[®]; Ajinomoto Pharma, Tokyo, Japan) on the morning of or night before the examination for bowel preparation. The insufflated gas was only CO₂, not room air. Each

Table 1. Specifications of Magnifying Endoscopes.

	EC-L590ZW	EC-L600ZP	EC-L600ZP7	CF-H260AZI	CF-HQ290I	PCF-HQ290ZI
Tip diameter (mm)	12.8	11.7	11.7	13.6	13.2	11.7
Soft part diameter (mm)	12.8	11.8	11.8	12.9	12.8	11.8
Effective length (mm)	1,330	1,330	1,330	1,330	1,330	1,330
Total length (mm)	1,630	1,630	1,650	1,655	1,680	1,680
Variable stiffness	Off	Off	On	On	On	On

Table 2. Baseline Participant Characteristics.

Characteristic	Total (n=600)
Age, mean±SD	62.92±13.01
Sex, male/female	386/214
BMI (kg/m²), mean±SD	22.54±4.00
History of abdominal surgery	35.5% (213)
Colectomy	9.8% (59)
Pelvic surgery	6.3% (38)
Gastrectomy	3.5% (21)
Previous colonoscopy	75.4% (447)
Indication	
Surveillance	35.4% (210)
Diagnosis without symptoms*	44.8% (269)
Diagnosis with symptoms**	20.4% (121)
Constipation	11.0% (65)
Irritable bowel syndrome	4.2% (25)

* positive fecal occult blood test and detected malignant tumor in the other organ. ** abdominal pain, bloody stool, constipation, and diarrhea.

endoscopist decided whether or not an endoscope tip hood or an antispasmodic agent was to be used. Hyoscine N-butyl bromide (Buscopan®) or glucagon was injected intramuscularly as an antispasmodic agent just before endoscope insertion. We measured and recorded the insertion time to the cecum and the withdrawal time using a stopwatch. The withdrawal time included the time required for magnified observation. When the endoscopist found insertion difficult, the assistant compressed the patient's abdomen, or the patient's position was changed.

Magnified observation was performed for polyps detected excluding high-confidence cases of hyperplastic rectosigmoid polyps. The JNET classification (9) was used for the diagnosis based on the magnifying endoscope with narrow-band imaging (NBI) or blue-laser imaging (BLI). Indigo carmine dye spraying was performed, not crystal violet dye spraying. If a pit pattern diagnosis on crystal violet staining was required, sedated colonoscopy was performed on another day. In the present study, endoscopic therapy (e.g. CP, EMR) was not performed, although biopsy specimens were taken. The polyps were resected endoscopically on another day in some cases. The histopathological diagnosis was based on the World Health Organization criteria.

Definitions

The magnifying endoscopes used are shown in Table 1. Endoscopes have two major features that can influence in-

sertion: variable stiffnesses and diameters. We defined small-diameter types as those <12 mm in diameter. Bowel preparation quality was assessed using the Aronchick bowel preparation scale (excellent: a small volume of clear liquid or >95% of surface visible; good: large volume of clear liquid covering 5-25% of the surface but >90% of surface visible; fair: some semisolid stool but >90% of surface visible; poor: semisolid stool could not be sucked away and <90% of surface visible; inadequate: repeat preparation needed) (31). Constipation was defined as fewer than three bowel movements per week for six months. Irritable bowel syndrome was defined as symptoms of recurrent abdominal disorder for at least six months based on the Rome III criteria.

Pain scale

Patient pain was assessed using an 11-point numerical rating scale. The scale ranged from 0 (no pain) to 10 (worst pain imaginable). We defined 5 as mild enough pain that patients would not be reluctant to undergo another colonoscopy. Acceptable pain was defined as 5 or less and severe pain was defined as 8 to 10. The patients described the pain intensity according to the scale immediately after the procedure.

Statistical analyses

Statistical analysis was performed using the SPSS 25 software program (IBM, New York, USA). Univariate and multivariate linear regression analyses with stepwise selection were performed using pain scale scores as the dependent variables and all other variables of interest as the independent variables. The related variables were tested for analyzed using the Mann-Whitney U test and the chi-square test. P values <0.05 were considered significant.

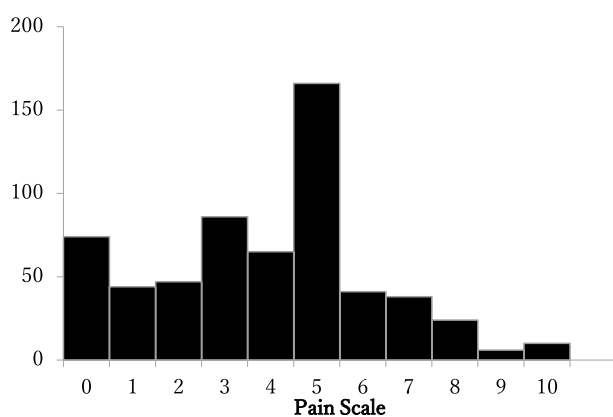
Results

A total of consecutive 600 unsedated colonoscopies were performed. The characteristics of these 600 cases are shown in Table 2. The mean patient age was 62.9±13.0 years old, 386 (64.3%) patients were men, 447 (74.5%) patients had undergone a previous colonoscopy, and 213 (35.5%) patients had a history of abdominal surgery, including 53 (9.8%) colectomies and 38 (6.3%) pelvic surgeries.

The performance parameters of the procedure are shown in Table 3. The complete insertion rate to the cecum was 99.5% (597/600). Insertion to the cecum was abandoned at

Table 3. Performance Parameters of Procedure.

Characteristic	Total (n=600)
Completion rate	99.5% (597)
Insertion time, minutes, mean±SD	6.44±4.11
Withdrawal time, minutes, mean±SD	14.59±5.07
Bowel preparation	
Excellent/Good	73.8% (218/225)
Fair/Poor	26.2% (116/41)
Antispasmodic agent	37.6% (223)
Hyoscine N-butyl bromide	32.7% (196)
Glucagon	4.5% (27)
Small-diameter endoscope	53.3% (320)
Function of variable stiffness	76.0% (456)
Tip hood use	20.9% (124)
Polyps present	47.4% (281)
Diverticulum	29.7% (176)
Pain scale score, mean±SD	3.88±2.38

**Figure.** The pain scale score.

the transverse colon in two cases and sigmoid colon in one case. A total of 176 diverticula were detected; of them, 95 were in the sigmoid colon. The characteristics of polyps detected are shown in Table 4. The polyp detection rate was 46.8% (281/600), the adenoma detection rate was 35.7% (214/600), and the colorectal carcinomas (CRC) (including intramucosal carcinomas) detection rate was 1.7% (10/600). The mean number of adenoma per positive participant (APP) was 2.2 (max 15), and the mean size of adenoma was 5.2±3.38 mm. Hyperplastic rectosigmoid polyps were seen in 21 cases.

The mean insertion time was 6.44±4.11 minutes, while the mean withdrawal time was 14.59±5.07 minutes. The pain scale score is shown in Figure. The mean pain scale score was 3.88±2.38, and the percentage of patients reporting a score of ≤5 (defined as acceptable pain) was 80.5% (483/600). The percentage reporting a score of ≥8 (defined as severe pain) was 6.7% (40/600), including the incomplete cases. In addition, we showed the performance parameters depending on presence of polyps (Table 5). The insertion time was not significantly different between the patients with and without polyps (6.62±3.98 vs. 6.29±4.21 minutes,

Table 4. The Characteristics of Polyps Detected.

Characteristics	Total (n=576)
Size	
≤5 mm	401
6-9 mm	115
10-19 mm	48
≥20 mm	12
Location	
Cecum	48
Ascending colon	121
Transverse colon	141
Descending colon	71
Sigmoid colon	155
Rectum	40
Shape	
0-Ip	26
0-Isp	32
0-Is	225
0-IIa	29
0-IIb	0
0-IIc	0
Advanced Carcinoma	2
Histological findings	
Hyperplastic polyps	114
SSA/P	4
Adenoma	447
Intramucosal carcinoma	11
Advanced carcinoma	2
Others	20

SSA/P: sessile serrated adenoma/polyp

respectively). The withdrawal time was significantly different between the patients with and without polyps (16.30±4.95 vs. 13.08±4.69 minutes). The mean pain scale scores were not significantly different between the patients with and without polyps (3.82±2.24 vs. 3.94±2.49).

A univariate analysis showed that the factors associated with pain were older age, colectomy, antispasmodic agent use, small-diameter endoscope use, and variable stiffness. A multivariate analysis revealed that an older age, history of colectomy, antispasmodic agent use, and small-diameter endoscope use were significantly associated with patient pain (Table 6). In addition, we showed the performance parameters depending on antispasmodic agent use and small-diameter endoscope use. The use of these factors can be intervened by endoscopist. The mean of pain scale score was significantly different between the groups with and without antispasmodic agent use (3.47±2.38 vs. 4.13±2.34, p=0.001), despite a relatively long withdrawal time (15.24±5.20 vs. 14.21±4.97 minutes, p=0.016) (Table 7). The mean pain scale score was significantly different between the groups with and without a small-diameter endoscope (3.61±2.28 vs. 4.20±2.45, p=0.002). Moreover, the groups with a small-diameter endoscope induces significantly more acceptable pain. (85.63% (274/320) vs. 73.93% (207/280), p=0.00003) (Table 8).

Table 5. Performance Parameters of Procedure Depending on Presence of Polyps.

	Polyp detected (n=281)	Polyp not detected (n=319)	p value
Insertion time, min, mean±SD	6.62±3.98	6.29±4.21	0.090
Withdrawal time, min, mean±SD	16.30±4.95	13.08±4.69	<0.01
Pain scale score, mean±SD	3.82±2.24	3.94±2.49	0.590
Antispasmodic agent use	40.92% (115)	33.86% (108)	0.095
Tip hood use	19.57% (55)	21.63% (69)	0.481

Table 6. Univariate and Multivariate Analyses of the Factors Associated with Pain.

Factor	Univariate analysis		Multivariate analysis	
	β -coefficient	p value	β -coefficient	p value
Older age (≥ 60 years)	-0.431 (-0.034 to 0.828)	0.033	-0.577 (-0.963 to -0.191)	0.003
Female sex	0.206 (-0.192 to 0.604)	0.310		
BMI (kg/m²)				
Low (<18)	0.152 (-0.565 to 0.868)	0.678		
High (≥ 25)	-0.099 (-0.554 to 0.357)	0.670		
History of abdominal surgery	-0.019 (-0.417 to 0.380)	0.926		
Colectomy	-1.265 (-1.898 to -0.633)	<0.001	-1.222 (-1.837 to -0.608)	<0.001
Pelvic surgery	0.478 (-0.305 to 1.260)	0.231		
Gastrectomy	-0.016 (-1.053 to 1.022)	0.977		
Previous colonoscopy	-0.185 (-0.622 to 0.252)	0.406		
Indication				
Surveillance	-0.356 (-0.755 to 0.042)	0.080		
Diagnosis without symptoms	0.083 (-0.300 to 0.467)	0.671		
Diagnosis with symptoms	0.376 (-0.098 to 0.850)	0.120		
Constipation	0.168 (-0.614 to 0.951)	0.673		
Irritable bowel syndrome	0.215 (-0.674 to 1.104)	0.635		
Bowel preparation (Excellent/Good)	0.011 (-0.423 to 0.444)	0.962		
Antispasmodic agent use	-0.657 (-1.048 to 0.266)	0.001	-0.717 (-1.096 to -0.338)	<0.001
Small-diameter endoscope use	-0.592 (-0.972 to -0.213)	0.002	-0.575 (-0.941 to -0.208)	0.002
Variable stiffness	0.507 (0.062 to 0.951)	0.026	0.053	0.215
Tip hood use	-0.181 (-0.652 to 0.290)	0.450		
Polyps detected	-0.120 (-0.502 to 0.261)	0.536		
Diverticulum	0.274 (-0.144 to 0.693)	0.198		

Table 7. Performance Parameters of Procedure Depending on Antispasmodic Agent.

	Antispasmodic agent (n=223)	Non-antispasmodic agent (n=377)	p value
Insertion time, min, mean±SD	6.49±4.69	6.42±3.72	0.842
Withdrawal time, min, mean±SD	15.24±5.20	14.21±4.97	0.016
Pain scale score, mean±SD	3.47±2.38	4.13±2.34	0.001
Acceptable pain rate	83.86% (187)	77.98% (294)	0.081
Severe pain rate	4.48% (10)	6.90% (26)	0.229
Polyp detection rate	51.57% (115)	44.56% (168)	0.096
Adenoma detection rate	39.91% (89)	33.15% (125)	0.095

Discussion

This study revealed patient pain and associated factors in unsedated colonoscopy using a magnifying endoscope. The mean numerical rating scale for pain was 3.88±2.38 on a 10-point scale, where a score of ≤ 5 was defined as acceptable pain. Furthermore, this study had a high completion rate, high adenoma detection rate, and adequate withdrawal

time (32, 33). The results revealed that unsedated colonoscopy using a magnifying endoscope generally involved acceptable patient pain.

The significant factors associated with painless colonoscopy using a magnifying endoscope were an older age, history of colectomy, antispasmodic agent use, and small-diameter endoscope use. Of these factors, we can proactively select antispasmodic agent use and a small-diameter endoscope before the examination.

Table 8. Performance Parameters of Procedure Depending on Small Diameter Endoscope.

	Small diameter endoscope (n=320)	Non-Small diameter endoscope (n=280)	p value
Insertion time, min, mean±SD	6.17±3.49	6.76±4.71	0.081
Withdrawal time, min, mean±SD	14.96±5.22	14.18±4.88	0.058
Pain scale score, mean±SD	3.61±2.28	4.20±2.45	0.0022
Acceptable pain rate	85.63% (274)	73.93% (207)	0.00003
Severe pain rate	4.37% (14)	7.86% (22)	0.073
Polyp detection rate	45.6% (146)	48.93% (137)	0.4186
Adenoma detection rate	34.06% (109)	37.5% (105)	0.3805

Some studies have previously reported that antispasmodic agent use reduces pain during colonoscopy (14, 27) because it inhibits intestinal movement, especially when moving the endoscope back to the anal area. In the present study, hyoscine N-butyl bromide or glucagon was used as an antispasmodic agent. The use of antispasmodic agents benefits patients, as they relax the bowel, facilitating the detection and observation of polyps and preventing any extra burden on the endoscopist related to missing polyps. Thus, we strongly recommend antispasmodic agents be used for unsedated colonoscopy.

Another factor, small-diameter endoscope, reduced pain because of the lower pressure applied to the intestinal tract than with a standard endoscope (15, 22). In addition, small-diameter endoscopes cause less stretching of the mesentery, one of the principal reasons for abdominal pain during colonoscopy. Even experts have found that patients feel significant pain with a short time to reach the cecum because of the high pressure placed upon the intestinal tract and stretching of the mesentery. In the present study, it was shown that a small-diameter endoscope was less likely to cause severe enough pain to make patients reject a subsequent colonoscopy. A recently developed small-diameter magnifying endoscope provides as sharp an image as a standard magnifying endoscope. Therefore, small-diameter endoscopes may be useful for unsedated colonoscopy.

In the present study, only experts performed the procedures; despite this, some patients still experienced severe pain with a long insertion time. Those who experienced severe pain will reject next colonoscopy for CRC. If the insertion time exceeds 10 minutes, it may be better to finish the procedure, use sedation, or change to another method, e.g., computed tomographic colonography or colon capsule endoscopy. We recommend using sedation in patients in whom insertion difficulty was previously encountered, as it is likely to cause severe pain that cannot be prevented by techniques, tools, and antispasmodic agents.

There was no significant difference in the mean pain scale score between examinations with and without colorectal polyps. The diagnosis of colorectal polyps using magnifying endoscopy, with reference to the JNET classification, required more time for a detailed observation than conventional observation. However, it did not cause more pain. Abdominal pain and fullness during withdrawal are usually caused by bowel distension associated with gas insufflation.

We used CO₂ in the present study, since it is absorbed faster than room air in all cases and causes less pain during withdrawal.

Several limitations associated with the present study warrant mention. First, it was performed by only experts in a single academic center. They learned the insertion technique by repeatedly withdrawing and straightening out the loops. Experts can often use abdominal completion and position change to ensure smooth insertion if necessary. Previous studies suggested that the factors responsible for painful colonoscopy were female sex, a low BMI, and a history of hysterectomy. In women and those with a low BMI, the angle of the sigmoid colon may be sharper. After hysterectomy, adhesions in the pelvis and sigmoid colon freely move because of the larger intra-pelvic space after surgery. Expert techniques might be extremely effective for ensuring adequate angles of the colon, suppression of free movement within the colon, and reduction of pressure on the adhesions. Second, the endoscope type, hood use, and antispasmodic agent use were decided by endoscopists, not randomly. Third, the degree of pain during colonoscopy varied among countries due to patient anxiety, the endoscopist's skill, insertion techniques, magnified observation techniques, and endoscopic equipment. Fourth, almost all detected polyps were <10 mm in size. The time required for magnified observation was not extended since we needed only one or two magnified images. If a lesion of >20 mm includes a carcinoma, more time might be required for the observation because of the larger surfaces for magnifying endoscopy.

In conclusion, unsedated colonoscopy using a magnifying endoscope by experienced endoscopist appears to be acceptable. Furthermore, the use of an antispasmodic agent, particularly hyoscine N-butyl bromide, and a small-diameter endoscope were recommended because they reduce pain during unsedated colonoscopy. The use of a magnifying endoscope may also be recommended in colonoscopy for colorectal cancer screening, although further studies will be required to clarify whether or not unsedated colonoscopy using a magnifying endoscope is acceptable in any condition.

The authors state that they have no Conflict of Interest (COI).

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