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Capsule endoscopy examination identifies different leading causes of obscure gastrointestinal bleeding in patients of different ages

Bing-Ling ZHANG, Chun-Xrao CHEN, You-Ming LI

Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, China

Background/aims: *We aimed to investigate the diagnostic applications of capsule endoscopy examination patients in obscure gastrointestinal bleeding and to analyze the etiology of obscure gastrointestinal bleeding in patients of different ages.* ***Material and Methods:*** *A total of 385 patients with obscure gastrointestinal bleeding, aged 17–91 years, were assigned into three groups as: elderly (>65 years), middle-aged (41-65 years) and young adults (17-40 years). Gastrointestinal examinations were carried out in each participant with the use of a capsule endoscopy diagnostic system.* ***Results:*** *Overall, the detection rates for positive capsule endoscopy findings in the elderly, middle-aged and young adult groups were 66.94%, 62.29% and 61.80%, respectively, and the diagnostic rates were 48.76%, 45.14% and 53.93%, respectively. No significant difference existed in either rate between the different age groups. The commonest pathological changes detected were vascular malformations, intestinal tumors, Crohn's disease, non-specific enteritis, and small intestine ulcer, but the distribution of these causes for obscure gastrointestinal bleeding varied between the different age groups. The top three common reasons for obscure gastrointestinal bleeding in the elderly group were vascular malformations, small intestine ulcers and small intestine tumors, while in the middle-aged group vascular malformation, small intestine tumor and non-specific enteritis were the most common. The young adults were most likely to have Crohn's disease, small intestine tumors or non-specific enteritis.* ***Conclusions:*** *Capsule endoscopy examination not only shows potential diagnostic value for obscure gastrointestinal bleeding, but it also helps to identify the leading causes of obscure gastrointestinal bleeding in all age groups.*

Key words: Obscure gastrointestinal bleeding, capsule endoscopy, age, diagnosis

Farklı yaştaki kaynağı bilinmeyen gastrointestinal sistem kanamalarının en sık görülen nedenlerinin kapsül endoskopi ile tespit edebilirliği

Amaç: *Nedeni bilinmeyen gastrointestinal kanamaların odaklarının tespit edilmesi ve kapsül endoskopinin bu kanamalardaki tanısal etkinliğinin incelenmesi amaçlanmıştır.* ***Yöntem ve Gereç:*** *Nedeni bilinmeyen gastrointestinal kanaması olan, 17-91 yaş arası toplam 385 hasta yaşlı (>65), orta yaşlı (41-65 yıl) ve genç erişkinler (17-40 yıl) olmak üzere 3 gruba ayrıldı. Her bir hasta kapsül endoskopi kullanılarak incelendi.* ***Bulgular:*** *Yaş gruplarına göre pozitif kapsül endoskopi bulunma oranları yaşlı, orta yaşlı ve genç erişkin gruplarında sırasıyla %66,94, %62,29 ve %61,80 olarak ve doğru tanısal oranları sırasıyla %48,76, %45,14 ve %53,93 olarak bulundu. Her iki oran açısından yaş grupları arasında anlamlı bir farklılık bulunmadı. En sık tespit edilen patolojiler, vasküler malformasyonlar, intestinal tümörler, Crohn hastalığı, non-spesifik enterit ve ince barsak ülserleri olarak bulundu, ancak bu patolojilerin yaş gruplarına göre dağılımı anlamlı olarak farklılıklar göstermekteydi. Yaşlı grupta en sık karşılaşılan nedeni bilinmeyen gastrointestinal kanama nedenleri vasküler malformasyonlar, ince barsak ülserleri ve ince barsak tümörleri olarak bulundu. Orta yaşlı grupta vasküler malformasyonlar, ince barsak tümörleri ve non-spesifik enterit olarak bulundu. Genç erişkin grubunda ise Crohn hastalığı, ince barsak tümörleri ve non-spesifik enterit olarak tespit edildi.* ***Sonuç:*** *Kapsül endoskopi incelemesi nedeni bilinmeyen gastrointestinal kanamalarda tanı koyma potansiyeline sahiptir ve tüm yaş gruplarında en sık karşılaşılan kanama nedenlerini ortaya koyabilmektedir.*

Anahtar kelimeler: Nedeni bilinmeyen gastrointestinal kanama, kapsül endoskopi, yaş, tanı

Address for correspondence: You-Ming LI
Department of Gastroenterology, the First Affiliated Hospital,
College of Medicine, Zhejiang University, Hangzhou 310003, China
Phone: 86-571-87236603 • Fax: 86-571-87080565
E-mail: liyouming79@163.com

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is generally characterized as persistent or recurrent GIB, which cannot be identified by conventional gastrointestinal endoscopy and/or conventional radiological examinations of the small intestine (1). Pathological changes in the small intestine account for 2-10% of all causes for OGIB; however, they are poorly identified by conventional approaches. As an emerging means of examination for OGIB, capsule endoscopy (CE) examination is becoming commonly used in practice and widely accepted by patients due to its noninvasive technique and direct vision of the intestine (2,3). The diagnostic rate of OGIB with CE examination varies from 38% to 93% (3-8), and the major pathological changes identified include vascular malformations, intestinal tumors, Crohn's disease, and non-steroidal anti-inflammatory (NSAID)-related enteropathy, amongst others, in previously reported studies (3-8). A meta-analysis has shown that CE is superior to push enteroscopy and small intestine barium radiography for the diagnosis of clinically significant small intestinal pathology in patients with OGIB. In the study populations, the incremental yield of CE over push enteroscopy and small bowel barium radiography for clinically significant findings is more than 30% with a number needed to test of 3, which was primarily due to the ability of CE to visualize additional vascular and inflammatory lesions directly (9).

In our previous study, we have also proven CE to be a safe, comfortable and effective procedure, with a high rate of accuracy for the diagnosis of OGIB. The rates of visualization of the entire small intestine and of clinically positive findings were 81.88% and 53.72% of cases, respectively (10). In addition, we compared the clinical efficacy of CE examination and multiple-detector computed tomography (MDCT) diagnostic imaging, which is another noninvasive diagnostic tool for small intestinal disorders, in the identification of OGIB. We found that the positive rate for CE (57.72%) was significantly higher than that of MDCT (30.08%). In addition, the detection rate due to the combination of CE and MDCT was significantly higher than that of MDCT alone. However, this was not significantly higher than that of CE alone, which suggested that the contribution of CE is critical in the diagnosis of OGIB (11).

However, limited evidence exists as to the diagnostic value of OGIB in patients of different ages. Secondly, it remains to be elucidated whether there are differences in the distribution of leading causes of OGIB in patients of different ages. Therefore, we initiated the current study, which aimed to determine the detection and diagnosis rates of CE examination from the results of its use in a large cohort of patients of varying ages with OGIB.

PATIENTS AND METHODS

Subjects

The recruitment criteria for the study subjects were described before in our previous report (11). A total of 385 patients with OGIB were recruited consecutively from June 2003 to November 2009 from the First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang Province in China. All of the study participants presented with hematochezia, chronic intermittent melena, or hypohemoglobinemia of varying severities and had a history of active (overt) hemorrhage within one week prior to the CE examination. A patient was considered to be suitable for inclusion into the study if the cause of GIB could not be identified by either gastroscopy or colonoscopy. Pregnant women, patients with pacemakers, and patients with intestinal obstruction were excluded from the study.

According to their ages, the included patients were divided into three groups, as elderly (>65 years [yrs]), middle-aged (41-65 yrs) and young adult (17-40 yrs). The study was approved by the Ethics Committee of Zhejiang University's First Affiliated Hospital and informed consent was obtained from each of the participants prior to their inclusion in the study.

Examination with Capsule Endoscopy

Capsule endoscopy (CE) examination in all the patients was carried out using a specified CE diagnostic system (Given Imaging Ltd, Yoqneam, Israel). All the subjects were fed a semi-liquid diet for 24 hours (h) and received complete colonic irrigation 12 h prior to the examination. They were deprived of water for 4 h and then given a defoamer orally 30 minutes (min) prior to the examination. Then, they were allowed to consume light beverages from 4 h after the capsule ingestion. During the examination, subjects were allowed to move freely, but were requested to avoid exposure to any strong electromagnetic field. Digital video image streams of the examination were downloaded to the Reporting and Processing of Images and Data (RAPID) workstation for graphic analysis.

One senior gastroenterologist with more than 10 years of clinical experience was assigned to review the CE examination results and to determine the location and characteristics of the lesions. The CE findings were classified as positive (observable sources of hemorrhage with the visualization of any attributable lesions, or signs of recent or active bleeding) and negative (no observable sources of hemorrhage, including active bleeding from a specific site without any sign of other lesions). A positive diagnosis was defined when the detected positive lesions by CE examination could explain the OGIB, and the diagnostic rates in each of the patient groups were then calculated.

Statistical Analysis

All data were analyzed with SPSS for Windows Software version 16.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were calculated for all clinical characteristics of the study subjects. All quantitative data with normal distribution were expressed as mean±SD; those that were not normally distributed were expressed as the median and quartile intervals. All qualitative data were expressed as a percentage of the subjects. The chi-squared test was used to compare two groups of qualitative data, with p values of <0.05 being considered as statistically significant.

RESULTS

Baseline Characteristics of the Subjects

A total of 385 patients with OGIB (193 males, 192 females), aged 17–91 years (54.6±16.4 yrs), whose course of disease varied from 3 days (d) to 18 yrs (median, 3 months [mo]), were enrolled in this study. Among them, 10 patients were noted to have fever, six had abdominal pain, four had weight loss, and one had diarrhea. In the elderly group, 18 patients had a history of hypertension, five had been diagnosed with coronary artery disease, and one had a history of cerebral infarction; in addition, four patients in this group described long-term use of aspirin, and another patient simultaneously took aspirin and clopidogrel. The baseline characteristics of the study participants are presented in Table 1.

CE Examination and Capsule Discharge

All 385 patients swallowed the capsule endoscope successfully. However, nine patients in the elderly group failed to finish the CE examination; seven patients had prolonged retention of the capsule in the esophagus or stomach, and the capsule in the other two patients failed to progress through the upper small intestine. The remaining 376 patients completed a full examination of the small intestine or stopped when lesions were found during the CE examination. After the examination, 17 patients had a delay in discharging the capsule through the intestine, which was mainly due to small intestine tumors or Crohn's disease. Among them, four patients with small intestine tumors and three patients with Crohn's disease underwent surgical removal of lesions during the same procedure as the capsule removal. All of the other patients with delayed capsule discharge had Crohn's disease, and they all discharged the capsule after formal treatment over a period of 20 d to 7 mo post-examination.

CE Examination Results

Detection rate and diagnosis rate in all subjects

Out of 385 patients, 376 (97.66%) had successful CE examinations. Positive lesions were detected by the CE in 245 patients, and the overall detection and diagnostic rates were 65.16% (245/376) and 49.47% (186/376), respectively.

Table 1. Baseline characteristics and history of pre-existing medical conditions of patients with OGIB (n=385)

	Elderly (n = 121)	Middle-Aged (n = 175)	Young Adult (n = 89)
Sex (M/F)	49/72	84/91	60/29
Age (years,$\bar{x}$ ± s)	74.1±5.1	55.3±7.1	29.8±6.8
Hb (g/L, range)	78.4 (52.3-118.2)	82.7 (61.3-129.3)	81.9 (70.4-130.1)
Patients that received transfusion (%)	45.12	43.51	23.35
Previous examinations			
Patients that received a small intestine enema	28/121 (23.14%)	22/175 (12.57%)	10/89 (11.24%)
Patients that underwent vascular contrast	2/121 (1.65%)	10/175 (5.71%)	6/89 (6.74%)
Patients that underwent nuclide scanning	3/121 (2.48%)	2/175 (1.14%)	0/89 (0.00%)
Patients that underwent push enteroscopy	1/121 (0.83%)	4/175 (2.29%)	1/89 (1.12%)

Detection rate and diagnosis rate in each group

No significant difference was found between the different age groups with regards to either the detection rate ($p>0.05$) or diagnostic rate ($p>0.05$). In the elderly group, the detection rate (81/121, 66.94%) was significantly higher than the diagnostic rate (59/121, 48.76%; $p<0.01$). A similar result was observed in the middle-aged group, where the detection and diagnostic rates were 62.29% (109/175) and 45.14% (79/175), respectively ($p<0.01$). There was no significant difference in the young adults group in the rates of detection (55/89, 61.80%) and diagnosis (48/89, 53.93%), respectively ($p>0.05$).

Distribution of positive lesions detected by CE examination in each group

In the elderly group, a total of 92 positive lesions were detected in 81 patients by CE examination, among whom nine patients had two lesions and one patient had three lesions. The number of lesions detected in the middle-aged and young adult groups was 112 (109 patients, among whom 3 patients had 2 lesions) and 55, respectively. The distribution of positive lesions detected by CE examination in each group is shown in Table 2.

Double-Balloon Enteroscopy Examination

A total of 19 patients underwent double-balloon enteroscopy (DBE) examination after the CE examination; 16 of these patients had positive lesions detected by CE examinations, among whom 10 patients were confirmed to have positive lesions through DBE examination. These included interstitialoma (n=3), vascular malformations (n=2), Crohn's disease (n=2), lipoma (n=1), lymphoma (n=1), and polyps (n=1). One patient who was shown to have lymphoma by the CE examination, which was not demonstrated by the DBE examination, was confirmed to have lymphoma by surgical examination; the other five patients (including 3 patients with vascular malformations, 1 patient with small intestine ulcer, and 1 patient with polyps) showed no positive lesions on DBE examination. In one of the 19 patients, a positive lesion was found to be ileal bleeding by CE examination and an ileal ulcer by DBE examination and was confirmed to be intestinal tuberculosis after a biopsy. No positive lesion was found in the other two patients by either the CE or DBE examinations.

Surgery and Prognosis

A total of 65 patients received surgical treatment, including 49 patients with small intestine tumors,

Table 2. Distribution of positive lesions detected by CE examination in each group

	Elderly		Middle-Aged		Young Adult	
Type of lesion	**n**	**Diagnostic yield of CE**	**n**	**Diagnostic yield of CE**	**n**	**Diagnostic yield of CE**
Vascular anomalies	50	54.35%	39	34.82%	5	9.09%
Crohn's disease	2	2.17%	8	7.14%	19	34.55%
Small intestinal tumors	11	11.96%	35	31.25%	13	23.64%
Stromal tumor	4	4.35%	21	18.75%	2	3.64%
Lymphoma	0	0.00%	2	1.79%	2	3.64
Hemangioma	0	0.00%	2	1.79%	4	7.27%
Lipoma	2	2.17%	0	0.00%	1	1.82%
Adenocarcinoma	0	0.00%	1	0.89%	0	0.00%
Migratory tumor	0	0.00%	2	1.79%	0	0.00%
Small intestine polyps	5	5.43%	7	6.25%	4	7.27%
Non-specific enteritis	10	10.87%	11	9.82%	6	10.91%
Small intestine ulcer	12	13.04%	10	8.93%	4	7.27%
Multiple	10	10.87%	6	5.36%	2	3.64%
Isolated	2	2.17%	4	3.57%	2	3.64%
Ancylostomiasis	4	4.35%	6	5.36%	0	0.00%
Small intestinal diverticulum	2	2.17%	2	1.79%	4	7.27%
Ischemic bowel disease	1	1.09%	0	0.00%	0	0.00%
Ileal lymphoid follicular hyperplasia	0	0.00%	1	0.89%	3	5.45%
Abdominal anaphylactoid purpura	0	0.00%	0	0.00%	1	1.82%
Total	**92**	**100%**	**112**	**100%**	**55**	**100%**

six with vascular malformations, two with Crohn's disease, three with a small intestine diverticulum, one with small intestine ulcer, and one with superior mesenteric vein thrombosis. Among them, two patients with vascular malformations and one with Crohn's disease bled again during the postoperative period; no rebleeding was found in the others. Those patients who did not undergo surgical treatment were given symptomatic medical treatment and were then followed-up in the clinic.

DISCUSSION

The diagnosis of OGIB was difficult before the advent of CE examination. Previously used conventional approaches for the investigation of small intestinal diseases included barium meal X-rays, push enteroscopy, radionuclide scans, and selective celiac angiography. However, there are several shortcomings in these methods, including low rates of positive diagnosis, less accuracy in determining the location of bleeding, and traumatic examinations with complications (12-15). CE examination constitutes a noninvasive approach that allows the direct vision of lesions in the small intestine, and it is becoming the first choice for OGIB investigation (16,17).

In the present study, participants in all age groups tolerated the CE examination well. However, nine patients in the elderly group failed to complete the examination. Seven of them showed prolonged retention of the capsule in the esophagus and stomach, which may have resulted from decreased esophageal and gastric motility or poor relaxation of the lower esophageal sphincter in older individuals. Therefore, it is necessary to consider the risk of esophageal and gastric retention when performing the CE examination in elderly patients. Capsules should be delivered directly into the duodenum using a gastroscope when necessary.

We found that the diagnosis of vascular malformations remains difficult with CE examinations. Vascular malformations could sometimes be clearly identified as the cause of small intestinal bleeding because they were very typical, accompanied by bleeding or confirmed by surgery. However, in most cases, small intestinal mucosal vascular tortuosity, expansion or tumor-like changes found by CE examination could not be confirmed as the reasons for bleeding. Small intestine tumors that manifested within intracavity protrusions, ulcers or infiltrative changes could be diagnosed according to the form, color and range of those lesions. CE examination exerted relatively high diagnosis rates of Crohn's disease, which can help indicate the type (such as ulcers form, fistula, stricture, or degree of pebble-like changes) and scope of this kind of disease. It is noteworthy that the differential diagnosis of other diseases with ulcerating changes, such as intestinal tuberculosis and NSAID enteropathy, should not be ignored.

Non-specific enteritis in the CE examination was mainly manifested by congestion and edema in the small intestinal mucosa or was accompanied by superficial erosions. Most of the diagnosed small intestine multiple ulcers were small or point-like ulcers. Four of the patients with small intestine multiple ulcers underwent a reexamination by CE between one and three years after the first diagnosis; the ulcer disappeared in three of them (2 were treated by 5-aminosalicylic acid for 3-6 months and the other patient did not receive drug treatment). In addition, CE examination could visualize hookworms clearly, including their shape and number. For the diagnosis of diverticulitis, CE examination results may be biased by the chance of encountering the point of diverticular openings. For the cases of superior mesenteric vein thrombosis, we diagnosed this condition through observing segmental changes of the small intestine, color changes in the junctional mucosa, mucosal congestion and edema in the entire segment, and cellulose exudation at the surface. Unfortunately, in the cases of ileal lymphoid follicular hyperplasia, CE examination could only identify the lesions but could not confirm whether or not they were the reason for bleeding.

In our study, the overall detection and diagnostic rates by CE examination were 65.16% and 49.47%, respectively. These rates were consistent with previous studies and significantly higher than results from gastrointestinal imaging and push enteroscopy (2-9). The p value for differences in the detection and diagnostic rates between the different age groups was non-significant, which suggests that CE examination has good detection and diagnostic capacity for OGIB in individuals of various ages. On the other hand, the detection rate was significantly higher than the diagnostic rate in the elderly and middle-aged groups because certain vascular malformations were excluded due to uncertain diagnosis as the cause of bleeding, although they were detected in these groups. In our experience, CE examination findings combined with a body surface road map analysis might

have great value for identifying the location of bleeding, which could help determine the location of DBE examination and the site of surgical exploration.

Although it was reported that vascular malformations, small intestine tumors, and inflammatory bowel disease were the main reasons for OGIB, we found that the main causes of OGIB were not the same in the different age groups. In this study, the three commonest reasons for OGIB in the elderly were vascular malformations, small intestine ulcers and small intestine tumors. The patients in the middle-aged group were most commonly affected by vascular malformations, small intestine tumors and non-specific enteritis, and the young adults were most likely to be affected by Crohn's disease, small intestine tumors and non-specific enteritis. Vascular malformation had the highest rate of detection in elderly patients, which correlates with the common prevalence of vascular sclerosis in elderly people. When vascular malformation is difficult to confirm as the cause of bleeding, a repeated CE examination or DBE examination should be considered. Moreover, multislice spiral CT could also be considered for patients with small intestinal bleeding, because small intestine tumors are in the top three common causes of intestinal bleeding in all age groups. This type of examination can not only identify small intestine tumors, but also determine the anatomical relationship between the tumor, intestinal wall, outside cavity mesangium, and blood vessels, which assists in the planning of surgical management (11).

In the young adult group, Crohn's disease was the most commonly detected pathology. It should be noted that some patients with Crohn's disease had capsule retention. Although most of them could ultimately discharge the capsule after treatment, some needed surgical treatment to discharge the capsule.

In summary, our study demonstrated that CE shows potential diagnostic value in patients with OGIB across different age groups. Vascular malformations, small bowel tumors and Crohn's disease were the principal causes of OGIB in this Chinese population, but it should be noted that their distributions between the different age groups were not the same.

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