

The Role of Capsule Endoscopy, Balloon-Assisted Enteroscopy and Clinical Parameters in the Management of Patients with Obscure Gastrointestinal Bleeding

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ABSTRACT

AIM: Capsule endoscopy is the first-line diagnostic method for patients with obscure gastrointestinal bleeding, however a substantial number has non-diagnostic findings. Our aim is to determine the role of capsule endoscopy, balloon-assisted enteroscopy and clinical parameters in the management of patients with obscure gastrointestinal bleeding.

MATERIALS AND METHODS: 578 patients were included in this retrospective study. Capsule endoscopy and balloon-assisted enteroscopy results were classified as diagnostic (positive) or non-diagnostic (negative). Clinical variables were analyzed to find predictors associated with rebleeding within 2 years.

RESULTS: Capsule endoscopy was classified as diagnostic in 160 (28%) patients, including 8 small bowel tumors. The diagnostic yield of balloon-assisted enteroscopy guided by a positive capsule examination was significantly enhanced towards 74% (52/70). A

Hb level of ≤ 5.0 mmol/L was an independent factor associated with an increased risk for rebleeding after a negative capsule examination (hazard ratio= 4.375 [2.859-6.696] ($p < 0.001$)). The success rate of a diagnostic capsule endoscopy and risk for rebleeding were both significantly lower in premenopausal women with occult blood loss compared to postmenopausal women (9% vs 25%, $p = 0.017$) (5% vs 22%, $p = 0.009$).

CONCLUSION: Balloon-assisted enteroscopy should be used as a complementary procedure when guided by a diagnostic capsule endoscopy. If capsule endoscopy is non-diagnostic, additional examination is recommended in patients who present with a low Hb at onset of obscure gastrointestinal bleeding to prevent rebleeding. Occult bleeding in premenopausal woman is a poor indication for further gastrointestinal examination after conventional endoscopy.

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Key Words: Obscure gastrointestinal bleeding; Capsule endoscopy; Balloon-assisted enteroscopy; Double-balloon enteroscopy; Rebleeding

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) represents about 5% of all gastrointestinal hemorrhages^[1]. It is defined as bleeding of unknown origin that persists or recurs after endoscopic examinations of the upper and lower GI tract. OGIB is divided

into 2 subcategories; clinically overt GI bleeding like melena or hematemesis and occult bleeding defined as unexplained iron deficiency anemia and/or a positive fecal occult blood test result^[2]. In more than 80% of patients, OGIB originates in the small bowel^[3].

Capsule endoscopy (CE) is widely accepted as the first-line diagnostic modality for OGIB. It is a non-invasive method which provides a diagnostic yield of 32 to 83%^[4-5]. CE has been demonstrated to be superior compared to other modalities such as push enteroscopy^[6] and CT-enteroclysis^[7]. Nonetheless, a substantial number of patients with OGIB have non-diagnostic CE findings. There have been several studies that investigated the long-term outcome in terms of rebleeding in this specific group. Although some studies reported a recurrence of bleeding in 6 to 11% of patients^[8-9], other studies documented rates between 28 and 36%^[10-11]. This inconsistency is probably due to a large variance in studies design and different definitions of diagnostic CE findings.

Balloon-assisted enteroscopy (BAE) provides a diagnostic yield comparable with CE in the evaluation of OGIB^[12-15]. In addition, it offers therapeutic options. However BAE is an invasive and time-consuming procedure. There is still no consensus about the diagnostic value of subsequent BAE after a non-diagnostic CE^[14,16-17]. Currently, the American Gastroenterological Association (AGA) recommends follow-up and, if necessary, a second examination by CE or enteroscopy after a non-diagnostic CE^[2].

The purpose of this study was to determine the role of CE and BAE in the management of patients with OGIB. Based on clinical parameters, we tried to identify the risk factors associated with rebleeding after a prior non-diagnostic CE.

METHODS

Patients

All patients with OGIB referred to our unit for CE examination were enrolled between January 2008 and December 2013. They all had recently undergone an upper and lower well-prepared GI endoscopy with negative results. Exclusion criteria were age younger than 18 years, chemotherapy at the time of OGIB and patients who underwent BAE before CE. Only the first CE examination was included in this study. We analyzed patient data by reviewing their medical records. The lowest hemoglobin (Hb) level in 3 months preceding CE was registered. A recurrent bleeding was defined as bleeding at least 1 day after CE examination without further treatment or 1 day after undergoing targeted treatment. It was determined by evidence of recurrent visible passage of blood (melena, hematochezia or hematemesis) or an unexplained drop of hemoglobin (2g/dL or more from the baseline). The present study was reviewed and approved by the institutional review board. Informed consent was obtained from each patient before the procedure(s).

Capsule endoscopy procedure

CE was performed with a M2A[®] or SB3[®] capsule (PillCam, Given Imaging, Yoqneam, Israel). According to our unit's protocol, a clear liquid diet 24 h prior to examination and bowel preparation conducted with 1 L of PEG-based solution at least 16 h before examination was given. Patients were allowed to eat without dietary restrictions six hours after the capsule was swallowed. If the capsule remained in the stomach, a new capsule was placed endoscopically in the duodenum. All video recordings were reviewed by 1 of the 3 gastroenterologists with experience of more than 200 cases of CE interpretations. According to standard practice guidelines¹⁸, an abnormal finding was defined as a P2 lesion if it was considered as an explanation for OGIB

or if blood (clots) were presented in the lumen of the small bowel. If an abnormality was identified, but not thought to be the cause or provided insufficient explanation for OGIB, it was assigned a P1 status. Examinations that showed 1 or more P2 lesions were reported as studies with positive results, whereas those with only P1 lesions or no abnormality (P0) were reported as negative results. Subsequent treatment based on the result of CE was classified as targeted therapy if it treated the cause of OGIB and was conducted within 90 days after CE. These included interventions such as surgical resection, endoscopic hemostasis (e.g. argon plasma coagulation (APC), polypectomy) as well as medical therapies (e.g. discontinuation of anticoagulants, proton pump inhibitors for peptic ulcerations). Treatments were classified as nonspecific if the intended goal was purely symptomatic such as blood transfusion or iron replacement.

Balloon-assisted enteroscopy procedure

BAE was performed by using double-balloon enteroscopy (Fujinon, Inc, Saitama, Japan) or single-balloon enteroscopy (SIF-Q180 Olympus, Japan) enteroscopes. They were used in a random manner. We used the standard BAE method for insertion, withdrawal and observation, as described previously^[19]. For BAE, patients were kept fasting at least 8 h prior to examination. For antegrade BAE and retrograde BAE, bowel preparation with respectively 1 and 2 L PEG-based solution were used. Intravenous midazolam and fentanyl were used to conduct conscious sedation under monitored circumstances. If the proposed lesion was not reached, an ink tattoo was applied to mark the maximum insertion depth reached. The alternative route was examined within a short period of time depending on request of the referring physician.

For a good comparison, only the BAE procedures within 3 months were considered as subsequent after prior CE examination. Findings were defined as positive results if it was likely the cause of OGIB (e.g. tumor, arteriovenous malformation (AVM), ulcers, Meckel's diverticulum). Others were assigned as negative results.

RESULTS

A CE procedure was performed in 856 patients during the study period. Thirty-eight patients were excluded from analysis on the basis of our exclusion criteria. Another 240 patients were excluded, because they were referred only for CE examination while follow-up and further management was performed in referring centers. As a result, 578 patients were included in this analysis. The baseline characteristics of the study population are presented in Table 1. The complete small bowel was visualized in 522 patients (90%). CE procedure provided a diagnostic yield of 28%. These patients ($n=160$) were significantly older, had a lower initial Hb, more often an overt OGIB and history of cardiac disease than those with negative CE results ($p=0.000-0.004$). A diagnostic CE in premenopausal women with an occult bleeding at onset of OGIB was established in 9% (5/53) which was significantly lower in comparison with 25% of postmenopausal women (53/216) ($p=0.017$, Chi-squared test).

CE findings

Angiodysplasia of the small bowel accounted for 41% of positive CE findings ($n=65$). Other findings included active blood loss of unknown cause ($n=32$), suspected tumors ($n=17$), irregular aspect of mucosa ($n=15$), ulcers ($n=15$), colon pathology ($n=12$), gastric pathology ($n=3$) and polyps ($n=1$). The final diagnoses in cases of suspected tumors were as follow: a malignant tumor in 6 patients (1 carcinoid, 2 adenocarcinoma, 1 angiosarcoma, 1 metastatic melanoma

Table 1 Clinical characteristics of patients with OGIB.

Variables	Negative CE (n=418)	Positive CE (n=160)	Total (n=578)	P-value
Sex (male/female)	194 / 224	88 / 72	282 / 296	N/S*
Age (years +/-SD)	67.6 +/-13.9	71.8 +/- 12.9	68.8 +/- 13.7	0.001**
65 years at onset of OGIB (</>)	159 / 259	40 / 120	199 / 379	0.003*
Menopause (pre/postmenopausal)†	49 / 175	6 / 66	55 / 241	0.010*
Type of OGIB (n, %)				
Overt	42 (10)	52 (32)	94 (16)	<0.001*
Occult	175 (90)	108 (68)	484 (84)	
Medication used (n, %)				
PPI	264 (63)	113 (71)	377 (65)	0.066*
NSAID	31 (7)	12 (8)	43 (7)	N/S*
VKA	94 (22)	45 (28)	138 (24)	N/S*
TCI	167 (40)	71 (44)	238 (41)	N/S*
Comorbidity (n, %)				
Vascular	32 (8)	14 (9)	46 (8)	N/S*
Cardiac disease	159 (38)	86 (54)	245 (42)	0.001*
CVA	24 (6)	9 (6)	33 (6)	N/S*
Liver cirrhosis	8 (2)	5 (3)	13 (2)	N/S*
DM	125 (30)	47 (29)	172 (30)	N/S*
Dialysis	2 (0)	2 (0)	4 (0)	N/S*
Lowest Hb value before CE (mmol/L +/-SD)	6.1 +/- 1.3	5.3 +/- 1.3	5.9 +/- 1.3	<0.001**
Hb 5.0 (</>)	90 / 328	75 / 85	165 / 413	<0.001*
Follow-up in months (median +/-SD)	37.9 +/-20.6	34.6 +/- 21.7	37.0 +/-20.9	N/S**

†Cut-off point at 54.3 years^[20]; *Chi-squared test; **Unpaired t-test; N/S = not significant. SD = standard deviation; Hb = hemoglobin; OGIB = obscure gastrointestinal bleeding; CE = capsule endoscopy; PPI = proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drugs; VKA = vitamin K antagonist; TCI = thrombocyte coagulation inhibitor; Vascular = peripheral vascular disease; Cardiac disease = atrial fibrillation, myocardial infarction, known ejection dysfunction; DM =diabetes mellitus type 1 / 2.

and 1 metastatic squamous cell carcinoma) and 2 hemangiomas. Nine patients suspected to have tumors were proved to have a different diagnosis at enteroscopy: 2 cases of AVM's, 1 diverticulum, 1 bulbitis and 5 cases without abnormalities.

Targeted therapy after positive CE was as follow: Fifty-two patients had endoscopic hemostasis (using APC or clips in 48 cases and 4 polypectomies), 10 patients underwent partial small-bowel resection and 16 patients had changes in medical therapy including 5 who stopped anticoagulants. Although a positive CE result, 82 patients did not received targeted therapy: Twenty-two patients underwent additional examination without any lesions which could explain OGIB, in the remaining the initial approach of OGIB was symptomatic or expectant because of a mild anemia or a high rate of comorbidity.

Despite a non-diagnostic CE, 43 out of 418 patients received a sort of targeted therapy as a result of recurrent bleeding within 90 days or suspicion for a lesion by subsequent examination, others than CE. Three patients received endoscopic treatment (1 APC, 1 polypectomy, 1 RBL) for lesions situated outside the small bowel, 6 patients had undergone a surgical intervention (4 small bowel resections, 2 corrections of a hiatal hernia). The remaining had a change in medicine, including 10 patients who stopped anticoagulants.

CE followed by BAE

Seventy BAE were performed after a positive CE result with a mean time interval of 38 days (range 1-80) (Figure 1). The diagnostic yield of BAE guided by a positive CE result was 74% (52/70). Thirty-four BAE were conducted after a negative CE with a mean interval time of 56 days (range 5-91 days). An incorrect result of CE was discovered in 3 cases (2 AVM's and 1 GIST). No diagnosis was confirmed by BAE in the remaining 31 patients with a negative CE result.

Follow-up

The mean follow-up was 37.0 months (IQR 17.9-53.9). Twenty-seven percent of patients (158/578) experienced 1 or more rebleeding episodes within 2 years. The median time to rebleeding was 7.8 months (IQR 1.8-12.7). Among 82 patients with positive CE

examination who received no further treatment, the rebleeding rate during follow-up of 2 years was 38% (31/82) whereas in case of negative CE examination, 24% (91/375) of patients experienced a rebleeding (Figure 2-3). The difference in cumulative risk of rebleeding between these groups was statistically significant ($p=0.002$, log-rank test). Endoscopic hemostasis by APC or clips, during a maximum of three therapeutic sessions within 90 days, had the lowest success rate with 48% (23/48) of patients experiencing rebleeding within two years.

There was a spontaneous resolution of OGIB in 76% of cases after a negative CE (Figure 2). Since menstrual blood loss is a common cause of anemia and can be confused with OGIB, a subgroup analysis of women with occult bleeding at onset of OGIB was performed ($n=192$). Three cases of premenopausal women were excluded because an intrauterine device (IUD) was placed, considered as a specific treatment for anemia. Five percent of premenopausal women (2/43) experienced a recurrence of anemia versus 22% of postmenopausal women (33/149). This difference was statistically significant ($p=0.009$, Chi-squared test).

In two cases of those with initial non-diagnostic findings on CE, a small bowel tumor was missed. The diagnosis of GIST in the small bowel was made in 2 patients after respectively 5 days by DBE and 20 days by CT-scan. The reason for further evaluation was persisting anemia with a drop of hemoglobin. Both patients underwent a successful partial resection of the small bowel. During follow up, 1 patient died because of cardiac failure. The other is still disease-free.

Clinical parameters

Patients with a negative CE result without further treatment were analyzed to predict factors associated with rebleeding ($n=375$). The Cox proportional hazards analysis showed that a Hb ≤ 5.0 mmol/L at onset of OGIB was independently associated with an increased risk for rebleeding after a negative CE ($p<0.001$, hazard ratio 4.375) (Table 2). Univariate analysis was repeated for patient age, changing the threshold from 60 to 80 years in 10-year increments, but an advanced age was not found to be independently associated with risk of rebleeding, even as other parameters considered during our survey.

Table 2 Univariate and multivariate analysis for risk factors associated with rebleeding after negative CE without specific treatment.

Variables	Negative CE without further treatment (n=375)		Univariate analysis P-value	Multivariate analysis P-value	Hazard ratio	95 % CI
	No rebleeding n= 284 (%)	Rebleeding n=91 (%)				
Sex (male)†	117 (41)	52 (57)	0.013	0.298	1.258	0.817-1.938
≥65 years†	167 (59)	69 (76)	0.018	0.093	1.592	0.925-2.741
Type of initial bleeding (overt)†	19 (7)	16 (18)	0.010	0.461	1.232	0.707-2.148
Medication used						
PPI†	174 (61)	64 (70)	0.042	0.904	0.972	0.609-1.551
NSAID	26 (9)	5 (6)	0.331	N/A	N/A	N/A
VKA	54 (19)	17 (19)	0.773	N/A	N/A	N/A
TCI†	98 (35)	47 (52)	0.027	0.526	1.156	0.739-1.807
Comorbidity						
Vascular	21 (7)	8 (9)	0.795	N/A	N/A	N/A
Cardiac disease†	96 (34)	46 (51)	0.005	0.092	1.486	0.938-2.356
CVA†	12 (4)	10 (11)	0.017	0.162	1.630	0.821-3.235
DM	80 (28)	31 (34)	0.468	N/A	N/A	N/A
Liver cirrhosis	3 (1)	2 (2)	0.851	N/A	N/A	N/A
Dialysis	2 (1)	-	-	N/A	N/A	N/A
Hb ≤5.0mmol/l†	33 (12)	42 (46)	<0.001	<0.001	4.375	2.859-6.696

†Variables with p-value less than 0.2 were included for multivariate analysis. CI = confidence interval; N/A = not applicable; PPI = proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drugs; VKA= vitamin K antagonist; TCI = thrombocyte coagulation inhibitor; DM= diabetes mellitus type 1 / 2; Cardiac disease =atrium fibrillation, myocardial infarct, known ejection dysfunction.

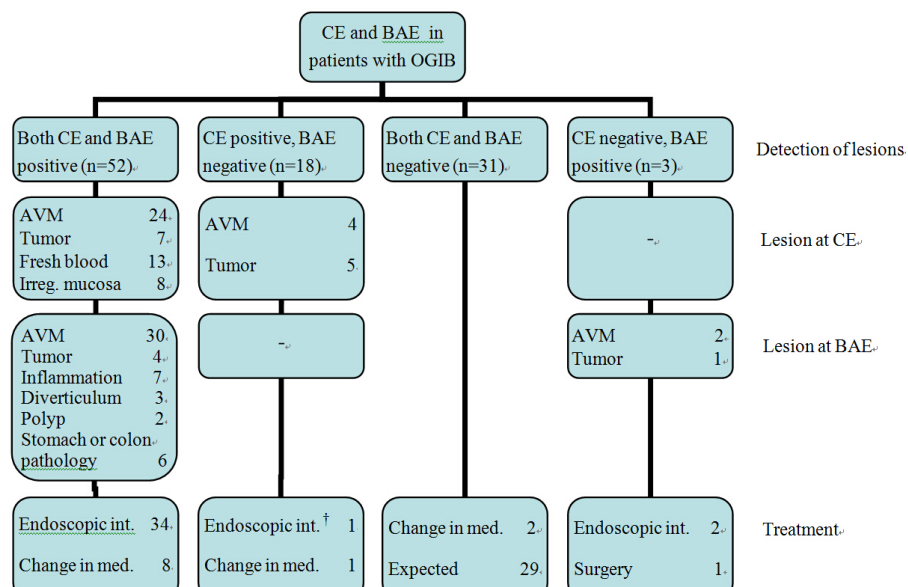


Figure 1 Patients with obscure gastrointestinal bleeding undergoing capsule endoscopy and complementary balloon assisted enteroscopy within 3 months. †GDS with argon plasma coagulation of lesions situated in the stomach.

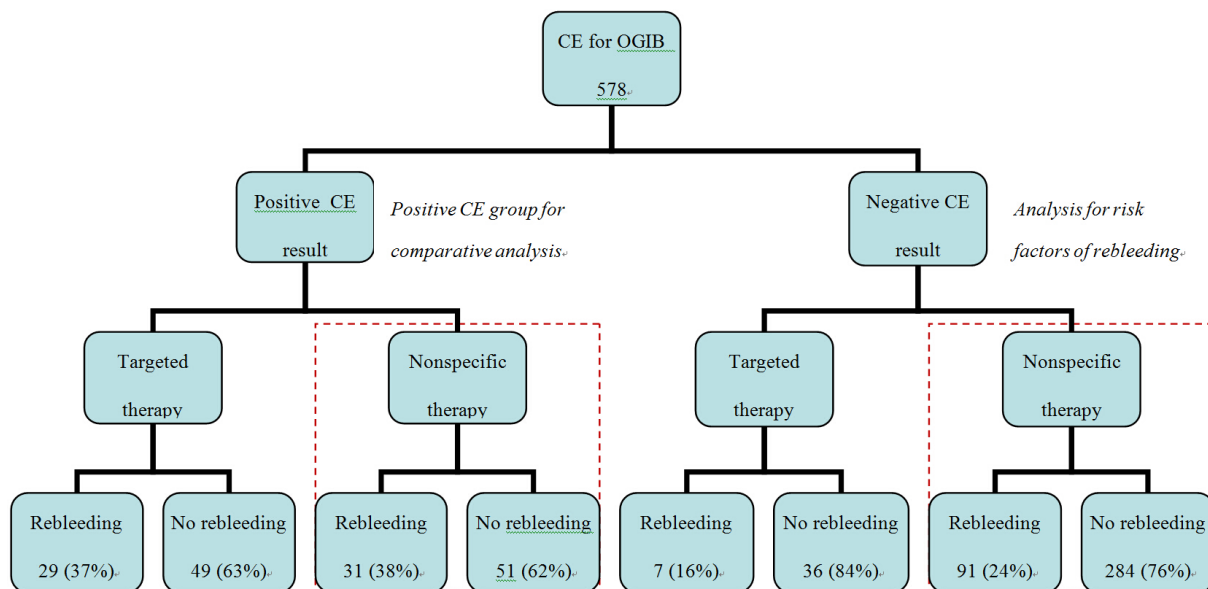


Figure 2 Clinical course of 578 study subjects with subgroups marked for analysis of risk for rebleeding.

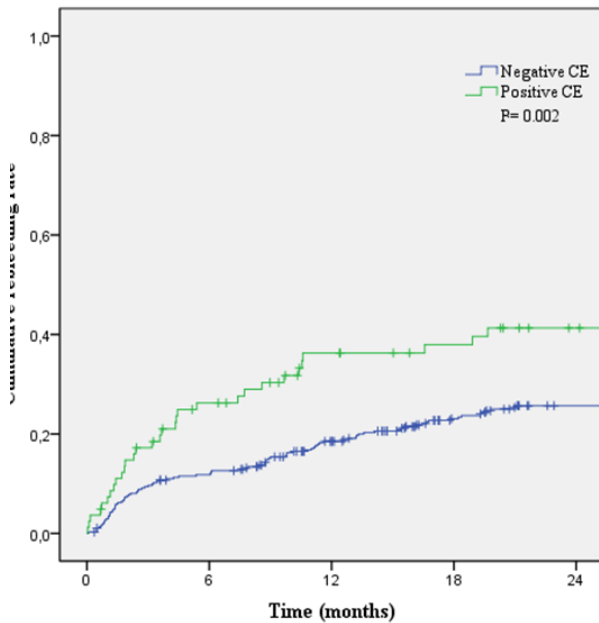


Figure 3 Cumulative rebleeding rates of patients without specific therapy according to the results of CE. The difference was statistically significant ($p=0.002$, log-rank test).

Tolerance and adverse events

Capsule retention was observed in 12 out of 578 procedures, all were subsequently retrieved endoscopically. No procedure related complications after BAE were noted in the present study.

DISCUSSION

This retrospective study offers long-term data on patients with OGIB who underwent CE with or without subsequent BAE. A diagnostic yield of 28% of CE was found. Although the diagnostic yield of 32–83% reported in various studies is higher^[4–5], an explanation might be the different definition of a positive finding on CE. In most of the studies all abnormalities were considered to contribute to the diagnostic yield whereas in our study only lesions with a clear causal relation to the intestinal bleeding were assigned a positive result.

To interpret the impact of CE in OGIB, a distinction has to be made between the direct and indirect value of CE. A CE directly influences the outcome of patients in a favorable way if it detects significant lesions that are treated successfully. In a total of 578 patients, 8 tumors were detected by a first CE procedure, including 6 malignant tumors. Two cases of small bowel tumors missed on CE examination were documented in this study with a diagnostic delay of at most 20 days which makes it unlikely that the false negative result of CE affected clinical outcome. Nevertheless, the potentially serious consequences must be taken into consideration. Various studies reported significant small bowel lesions missed by different modalities^[21–22]. In a meta-analysis of Lewis *et al*^[23] that included 24 studies and over 500 patients, a miss rate by CE of 18.9% for small bowel tumors was reported. Comparative methods had an even higher miss rate with a mean of 63.2%. So despite the improvement in small bowel visualization by CE, the miss rate for mass lesions is still unacceptable high. There are several possible explanations. Technical factors (a lack of air insufflation caused by angulated or collapsed lumen), a rapid capsule transit caused by more brisk peristalsis in especially the proximal small bowel^[24] and the fact that a tumor is usually unifocal which makes it harder to detect, all attribute to a risk of missed lesions

by CE. Therefore, depending on the clinical suspicion (history of malignancy, persistent GI bleeding, symptoms of obstruction), BAE or another form of small bowel visualization can still be needed.

We hypothesized that CE examination has an important role in guiding management of patients with OGIB. After comparative analysis of patients who had an expectant management, a significantly higher rebleeding rate after a positive CE (38%) versus a negative CE (24%) was found. This confirms that CE can be used as triage method in which a more aggressive management is desirable after a positive CE result. Targeted treatment after a positive CE result is assumed to result in less cases of rebleeding which can be considered as a direct consequence of CE procedure too. In our study, 37% of patients experienced rebleeding despite undergoing targeted therapy, whereas 63% of patients did not have a rebleeding episode anymore. This relatively disappointing outcome might be explained by the high percentage of AVM's which was the most common finding in our study. These lesions, initially treated successful by APC or clips, often need more therapeutic sessions^[25].

Indirect value of CE can be defined as selection of those patients where further diagnostic evaluation can be avoided, because a large number of spontaneous resolutions can be expected over a longer period. Although more rebleeding occurred after a positive CE result, recurrence of bleeding after a negative CE examination was still 24%. To predict which patients are likely to experience a rebleeding episode, there have been few studies. Matsumura *et al*^[16] reported that advanced age was a predictive factor for rebleeding after a negative CE. Kim and colleagues^[26] identified continued use of warfarin after initial bleeding as the only predictive factor. These conflicting results are partly due to the small numbers and a different follow-up duration of 1 and 3 years. To the best of our knowledge, our data provide the largest number of negative CE procedures followed for a longer period of time to document rebleeding rates. We found that a Hb level ≤ 5.0 mmol/L at onset of OGIB is an independent factor associated with more than four times higher risk of rebleeding.

Taken together, the use of anticoagulants and advanced age were predictive factors for rebleeding, however each of them alone was not an independent predictor.

Few studies tried to reveal which patients can be considered as a low-risk group for rebleeding. Hindryckx *et al*^[27] documented a high spontaneous resolution of anemia in premenopausal women with occult blood loss and suggested the importance of a gynecologic work-up in this group, however the numbers were small (6 premenopausal women) and no comparison with rebleeding rate in postmenopausal women was made. Another study of van Tuyl *et al*^[28] documented that CE only in 12% of premenopausal women led to a definite diagnosis compared to 31% in postmenopausal women. We found a definite diagnosis in only 9% of premenopausal women with an occult bleeding at onset of anemia. In addition, this subgroup had a significantly lower risk for rebleeding compared to postmenopausal women (5% vs 22%). This demonstrates that in accordance with earlier presumptions, a more expectant management in this particular group is appropriate.

BAE has a similar diagnostic yield as CE^[12–15] To investigate if subsequent BAE is beneficial in diagnosis of OGIB, a meta-analysis of 7 studies was performed by Teshima *et al*^[14] who reported a 75% diagnostic yield of BAE performed after a previously positive CE. This is in line with our results (74%). Both support the current algorithm of the AGA that CE could be used as screening modality in patients with OGIB and BAE can be recommended as second-line investigation with a considerably enhanced diagnostic yield after prior positive CE. This is likely due to the fact that CE guides

the endoscopist to choose the proper insertion route and provides information about the estimated distance and type of pathology. In 3 out of 34 negative CE cases, a subsequent BAE provided a definite diagnosis. Unfortunately, we could not assign predictors for this favorable outcome based on our data. A previous small study of Matsumura *et al.*^{16]} reported that the mean age of patients was significant higher in patients with a positive BAE compared to those with a negative BAE (71.0+/-7.9 vs 62.0+/- 16.9 years) (p<0.05). However, no multivariate analysis was done. More studies are needed for the true value of BAE after a negative CE and whether indication for subsequent BAE can be individualized.

The present study has certain limitations. It is known that the diagnostic yields of both CE and BAE are highest when performed within a short interval of anemia, especially in case of overt OGIB^[11,29-30]. Considering the retrospective nature of this study, the management was not in a standardized manner and time between onset of bleeding and CE is not known. Furthermore, although an arbitrary threshold of 3 months was used in our analyses, the time between CE and subsequent BAE was still relatively long.

CONCLUSION

Our study confirmed the leading role of CE in the diagnostic work-up of OGIB, because it is a non-invasive method for visualization of the entire small bowel and can direct further endoscopic interventions. BAE should be viewed as a complementary diagnostic procedure with a significantly enhanced diagnostic yield when guided by a positive CE result. In case of a negative CE result, additional diagnostic procedures are recommended in patients with a low Hb level at onset of OGIB. Occult bleeding in premenopausal women may be a poor indication for additional diagnostic procedures after conventional endoscopy. Subsequent BAE after a negative CE procedure might play an important role in avoiding miss diagnosis, especially in cases with ongoing bleeding or high suspicion of small bowel pathology. Since well-designed prospective studies are still missing, these findings, based on the largest long-term data collection of rebleeding ever reported, could help to improve the management of patients with OGIB.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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