RESEARCH ARTICLE

Factors predicting a positive capsule endoscopy in past overt obscure gastrointestinal bleeding: a multicenter retrospective study

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Abstract

Objectives: Capsule endoscopy (CE) remains the examination of choice for the investigation of obscure gastrointestinal bleeding. Although the factors predicting positive CE findings in the overall obscure gastrointestinal bleeding have been investigated, the clinical characteristics that predict a positive CE in patients with past overt obscure gastrointestinal bleeding (OOGIB) have not been systematically studied.

Methods: Between September 2004 and December 2013, 262 patients underwent CE for evaluation of past OOGIB after negative upper and lower endoscopy, and other diagnostic modalities. Patients' records were retrospectively reviewed to assess the factors that could possibly predict positive CE findings.

Results: Two hundred and twenty four patients with a median age of 70 years (range: 17-87) were enrolled in the final analysis and were divided into two groups; those who had positive (group A: 118 patients) and those who had negative CE findings (group B: 106 patients). The overall diagnostic yield of CE was 52.68 %. Multivariate analysis demonstrated that age >65 years, anticoagulant use, antiplatelet use, and non-steroidal anti-inflammatory drugs use were independent predictive factors for positive findings on CE. Of the 118 patients with positive CE, therapeutic interventions were performed in 56 patients (47.46 %). Recurrence of bleeding presented in nine patients of group B compared with 39 patients of group A ($p < 0.001$).

Conclusions: Certain clinical characteristics predict a positive CE in patients with past OOGIB. Patients with OOGIB and negative CE had a considerably lower rebleeding rate, and further invasive investigational procedures may be adjourned or may not be required, though such recommendation warrants further validation. Hippokratia 2016, 20(2): 127-132

Keywords: Past overt obscure gastrointestinal bleeding, capsule endoscopy, re-bleeding, predictive factors

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Introduction

Past overt obscure gastrointestinal bleeding (OOGIB) comprises about 5 % of all obscure gastrointestinal bleeds. It represents a significant economic burden with multiple studies attempting to optimize investigational algorithms through cost-effectiveness analyses. Moreover, it is a diagnostic challenge for all clinicians[1]. OOGIB has been defined as the passage of visible blood (melena or hematochezia) that recurs or persists despite negative initial endoscopic and radiologic estimations and is classified as active (ongoing) and past (inactive) gastrointestinal bleeding[2,3]. Recently[4], the former term referred to as obscure gastrointestinal bleeding (OGIB) was reclassified as small bowel bleeding. This change in terminology mainly reflects the decisive effect of advances in small bowel imaging [including capsule endoscopy (CE), deep enteroscopy, and radiographic imaging] on the identification of the origin of bleeding in the majority of patients. In the more recent definition, the term OGIB is reserved for cases in which bleeding's origin cannot be identified in the gastrointestinal (GI) tract and may represent a cause of bleeding outside the small bowel. However,

in the present study, the term OOGIB also includes small bowel bleeding being designed to investigate factors predicting a positive CE in patients with past OOGIB.

Several studies have investigated the factors predicting positive CE findings in the overall OGIB[5-9]. However, to the best of our knowledge, the clinical characteristics that predict a positive CE in patients with past OOGIB have not been systematically studied.

Patients and Methods

All patients presenting with the first episode of past OOGIB between September 2004 and December 2013, who underwent CE to identify the cause of bleeding at six centers of Northern (three), Central (one), and North-Eastern (two) Greece were included in the study.

According to the guidelines of the American Gastroenterological Association (AGA)[10], patients were defined as having past OOGIB when they had a history of visible bleeding episode (melena, hematochezia), followed by nondiagnostic upper and lower endoscopy.

Patients' records with past OOGIB were retrospectively reviewed: clinical and laboratory data were collected regarding age, gender, underlying diseases, use of anticoagulation, non-steroidal anti-inflammatory drugs (NSAIDs), or antiplatelet drugs, hematological profile (hemoglobin) at the time of CE examination, and time interval from the latest bleeding episode until CE examination. In addition, prior radiographic studies [abdominal computed tomography (CT) or magnetic resonance imaging (MRI), CT or MRI enterography, angiography] or other diagnostic modalities (^{99}Tc pertechnate scan) were also reviewed. In the current study patients with chronic renal failure undergoing regular hemodialysis or peritoneal dialysis were included.

CE was performed on an outpatient/inpatient basis after bowel preparation with oral administration of four liters of polyethylene glycol solution. Patients were allowed to drink clear fluid two hours after ingestion and were instructed to maintain their normal activities during CE examination. Outpatients returned to the hospital eight hours after capsule ingestion and the registration device and the antennas were collected.

The interpretation of lesions responsible for OOGIB was made according to CE structured terminology (CEST) described previously[11]. The findings were considered clinically significant if they could be the cause of gastrointestinal bleeding: angiodysplasias, ulcers, neoplasms, multiple erosions, Dieulafoy's lesion, hemangiomas, varices and aortoenteric fistulas. Findings such as small erosions, red spots, nonbleeding diverticula and nodules without mucosal breaks were inconsistent to potential bleeding and to record the CE as positive.

In the study only patients with excellent visualization (no debris, complete visualization of the mucosa) of whole small intestine were included. The recordings of CE were independently reviewed by six experienced endoscopists/gastroenterologists.

The patients were followed in the outpatient clinics or by telephone contact until the end of December 2013 to record rebleeding rate and clinical course. In cases of bleeding recurrence, CE was offered again when the cause of OOGIB had not been identified during the previous episode of bleeding. If upper gastrointestinal endoscopy and colonoscopy were performed in other centers [not participating in this study] and the etiology of the bleeding was identified, the diagnostic assessment was considered sufficient.

The primary endpoint of the study was to investigate the clinical characteristics that predict a positive CE after past OOGIB. A secondary endpoint of the study was to record the rebleeding rate of patients suffering from past OOGIB.

Statistical analysis

Categorical variables were analyzed with chi-square and Fisher's exact tests, as appropriate, while continuous variables were expressed as their median and ranges and analyzed using the Mann-Whitney U test. Possible predictive factors for positive CE were examined by univariate and multivariate analyses and acalculated with odds ratio (OR) with 95 % confidence interval (CI), using a logistic regression method. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Between September 2004 and December 2013, 262 patients underwent CE examination for investigation of past OOGIB. Of these, 224 patients (118 men, 106 women; median age 70 years, range 17-86) fulfilled the inclusion criteria and were included in the final analysis. The remaining 38 patients were excluded because 23 had incomplete CE examination and in 15 patients the data of their files were insufficient. CE was completed uneventfully in all patients without any capsule retention.

The patient population was divided into two groups; those who had positive (group A: 118 patients) and those who had negative (group B: 106 patients) CE findings (Table 1). Demographic characteristics of patients in both groups are presented in Table 1. There was a significant difference in the median age between group A and group B ($p = 0.001$) (Table 1). Thirty-two patients (14.29 %) were under anticoagulant (warfarin) treatment with a significant difference between the two groups (group A: 25 patients vs. group B: seven patients, $p = 0.009$) (Table 1). Fifty-three patients (23.7 %) were under antiplatelet treatment (clopidogrel and/or aspirin) with 43 patients being in group A and 10 patients in group B ($p = 0.007$) (Table 1). Forty patients (17.86 %) were under NSAIDs with a significant difference between the two groups ($p = 0.015$) (Table 1). There was no difference on hemoglobin at the time of CE examination and units of blood transfused. Time of CE examination and other imaging modalities used between the two groups were also studied (Table 1).

The overall diagnostic yield of CE was 52.68 % (n

Table 1: Clinical characteristics of the 262 patients with past overt obscure gastrointestinal bleeding who underwent capsule endoscopy between September 2004 and December 2013.

	Total n =224	Positive CE-Group A n =118	Negative CE-Group B n =106	p
Gender (Male/Female)	118/106	63/55	54/52	0.715
Age (years)	70 (17-87)	72 (18-87)	58 (17-83)	0.001
POGIB presentation				
Melena	176	92	84	0.852
Hematochezia	48	26	22	
Comorbid diseases				0.154
Coronary artery disease	82	75	7	0.025
Hypertension	62	50	12	
Diabetes mellitus	44	38	6	
Heart failure	23	20	3	
Heart valve disease	21	16	5	
Atrial fibrillation	23	20	3	
COPD	43	36	7	
Liver cirrhosis	10	10	0	
Chronic renal failure	8	6	2	
Stroke	16	14	2	
other	36	29	7	
Other imaging modalities used				0.0241
Enteroclysis	27	15	12	
Scintigraphy	16	7	9	
Angiography	9	4	5	
Abdominal CT	141	73	68	
Abdominal MRI	67	38	29	
CT enterography	17	11	6	
MRI enterography	13	8	5	
Medication used				0.087
Anticoagulant	32	25	7	0.009
Clopidogrel and/or aspirin	53	43	10	0.007
NSAIDs	40	27	13	0.015
Hb at time of CE examination (mg/dl)	11.9 (6.0-13.7)	10.1 (6.0-12.5)	12.6 (7.7-13.7)	0.084
Units of blood transfused	1 (0-3)	1 (0-3)	0 (0-3)	0.148
Time of CE examination after past-overt bleeding (Days)	10 (1-28)	8 (2-28)	12 (1-20)	0.032
Other imaging modalities used	111	83	28	0.072
Follow-up after CE (months)	16 (2-73)	14 (2-73)	16 (3-67)	0.214

Numbers represent number of patients or median and range (in brackets), n: number of patients, Hb: hemoglobin, CE: capsule endoscopy, POGIB: past overt gastrointestinal bleeding, COPD: chronic obstructive pulmonary disease, NSAIDs: non-steroidal anti-inflammatory drugs, CT: computed tomography, MRI: magnetic resonance imaging.

=118). The most common findings were angiodysplasias (54.24 %), followed by ulcers or multiple erosions (28.8 %), and tumors (8.47 %) (Table 2). Univariate and multivariate analyses of possible factors predicting a positive CE in patients with past OOGIB are demonstrated in Table 3. Multivariate analysis showed that age >65 years (OR 2.414, 95 % CI: 1.243-4.548, p =0.03), anticoagulant (OR 1.885, 95 % CI: 1.251-43.989, p =0.0014), antiplatelet (OR 1.934, 95 % CI: 1.334-4.219, p =0.012), and NSAIDs use (OR 1.645, 95 % CI: 1.154-3.564, p =0.023) were independent predictive factors for positive findings on CE (Table 3).

Of the 118 patients with positive CE findings, therapeutic interventions were performed in 56 patients (47.46 %)

Table 2: Etiology of past overt obscure gastrointestinal bleeding in the 118 patients with positive capsule endoscopy.

Disease	n =118
Angiodysplasia	64
NSAIDs-induced injury (ulcers, multiple erosions)	34
Tumors	
GIST	8
Adenocarcinoma	2
Carcinoid tumors	1
Portal enteropathy	6
Hemangioma	1
Post-radiation enteritis	2

n: number of patients, CE: capsule endoscopy, NSAIDs: non-steroidal anti-inflammatory drugs, GIST: gastrointestinal stromal tumor.

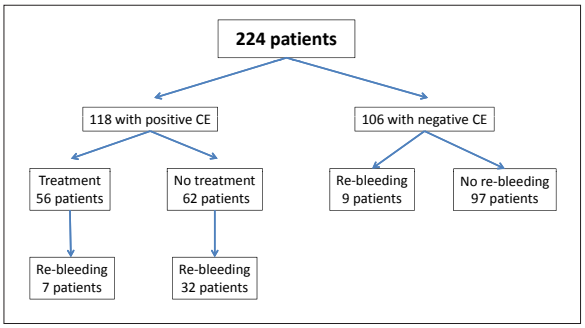

Figure 1: Flowchart showing patients' re-bleeding rate for the 262 patients in this study that underwent capsule endoscopy between September 2004 and December 2013 for investigation of past overt obscure gastrointestinal bleeding.
CE: capsule endoscopy.

Table 3: Possible factors predicting a positive capsule endoscopy in patients with past overt obscure gastrointestinal bleeding.

Variable	Univariate analysis			Multivariate analysis		
	p value	Odds ratio (OR)	95%CI	p value	Odds ratio (OR)	95%CI
Female sex	0.575	1.276	0.442 - 3-512			
Age >65 years	<0.001	3.254	1.356 - 6.438	0.003	2.414	1.243 - 4.548
Unit of blood transfused	0.148	1.853	0.643 - 4.324			
Anticoagulants' use	0.009	2.423	1.253 - 4.178	0.014	1.885	1.251 - 3.989
Antiplatelets' use	0.007	2.512	1.528 - 5.553	0.012	1.934	1.334 - 4.219
NSAIDs use	0.015	1.965	1.326 - 4.812	0.023	1.645	1.154 - 3.564
Time of CE examination after past-overt bleeding	0.032	2.143	1.344 - 5.618	0.073	1.532	0.856 - 3.958

GIB: Gastrointestinal bleeding, NSAIDs: Non-steroidal anti-inflammatory drugs, CE: Capsule endoscopy.

(Argon plasma coagulation in 16 patients, surgery in 19 patients, cessation of NSAIDs in 20 patients, and TIPSs application in one patient with Budd-Chiari syndrome and portal enteropathy).

With a median follow-up of 16 months, recurrence of bleeding was observed in 39 patients (33.05 %, 35 with angiodysplasias, one with radiation enteritis, three with portal enteropathy) with positive CE and in only nine patients (8.5 %) with negative CE (group B) (p <0.001) (Figure 1). In the latter group, of the nine patients that re-bled, only two accepted to undergo another capsule endoscopy after negative upper and lower GI endoscopy. In both patients, multiple small erosions were identified, in both cases related to NSAIDs use.

Discussion

The present multicenter retrospective study is the largest one that investigates the impact of clinical characteristics on the diagnostic yield of CE in patients with past OOGIB. The overall positive diagnosis of CE in our series was 52.68 %, lower than in other studies with OOGIB[12,13]. This is not surprising because most experts in CE have found that the maximized yield of CE is achieved when the examination is performed as close to the bleeding episode as possible[14,15]. In our study, the median time interval from the latest bleeding episode until CE examination was ten days, a time not too close to bleeding episode. Furthermore, a statistically significant difference of median time interval from the latest bleeding episode until CE between the two groups was observed (positive findings group vs. negative findings group, 8 vs. 12 days respectively, p =0.032).

In this study, patients under treatment with anticoagulants, NSAIDs and antiplatelets had a higher rate of positive CE (Table 1). Multivariate analysis showed that age>65 years and treatment with these drugs are the clinical characteristics that predict positive CE in patients with past OOGIB. Clinical characteristics including medications relevant to the diagnostic yield of CE in OOGIB have rarely been investigated to date. The correlation of angiodysplasias, the leading cause of bleeding in our and other reported studies, with advanced age is well-

known[16]; moreover, anticoagulants are well-recognized risk factors for gastroduodenal ulcers, postpolypectomy and postsphincterotomy bleeding and they probably have the same effect in patients with small intestine lesions[17-20]. Additionally, NSAIDs and aspirin are well-known causes of small intestine ulcers and multiple erosions which resolve upon withdrawal of the medications in most cases[21]. In our study angiodysplasias (54.24 %) were the leading cause of bleeding, followed by ulcers or multiple erosions and tumors, results which are comparable with other published studies[22]. Furthermore, we found a statistically significant difference in the re-bleeding rates between positive (33.05 %) and negative (8.5 %) CE findings ($p < 0.001$) (Figure 1), which is in accordance with the reports by Lai et al[23] and by Riccioni et al[24]. Our findings underscore the specificity of the negative predictive value of negative CE in patients with past OOGIB and are valid in the long-term follow-up.

Patients in the positive findings groups underwent significantly more other imaging modalities. A possible explanation could be that bleeding in these patients was more severe and/or prolonged; this cannot be established based on median hemoglobin level or number of blood units transfused. However, this may be due to the fact that patients in the positive findings group were significantly older with significantly more comorbidities, thus being more "fragile".

Taking into account that a significant number of patients with past OOGIB were under treatment with NSAIDs and the low re-bleeding rate in negative CE after a long-term follow-up we can limit the recommendations to perform CE in these patients and reduce the financial cost per patient. Nevertheless, before such recommendations become an established step in the management of patients with OOGIB and negative CE, sufficient evidence should be provided by future large-scale relative studies.

The main advantages of the current study are the large number of patients included and the long duration of follow-up. The main limitations are the retrospective design of the study and the inter-observer variability in the interpretation of CE findings of the centers involved. We also acknowledge that there is new AGA guideline[4] changing the classical term obscure GI bleeding; small bowel bleeding is not included anymore. In contrast, the term includes every GI bleeding that cannot be characterized as upper GI, colon or small bowel bleeding after performing extensively upper/lower GI endoscopy and CE. However this manuscript reports our clinical data from the period that CE had not yet been established as the gold standard method for assessing small bowel, therefore we used the older definition for OOGIB.

In conclusion, CE remains the leading examination in the investigation of past OOGIB. However, the selection of patients with high probability for positive CE could reduce the financial cost. Patients with OOGIB and negative CE had a considerably lower re-bleeding rate, thus further invasive procedures might be adjourned or might not be required in these patients, though such strategy requires further validation.

Conflict of interest

Authors declare no conflict of interest.

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