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Factors Related to Positive Finding of Capsule Endoscopy in Obscure GI Bleeding

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ABSTRACT

Background and Aims: Capsule endoscopy (CE) is used increasingly to identify causes of obscure gastrointestinal bleeding (OGIB). Identifying factors related to the detection of lesions by CE could improve resource utilization and patient selection for CE examination. We aimed to identify clinical factors related to positive findings from capsule endoscopy in OGIB.

Patients and Methods: We retrospectively analyzed 70 patients who underwent CE for overt and occult OGIB. Clinical factors that might be associated with positive CE findings were investigated.

Results: Our results showed a highly likely bleeding lesion (P2) in 18 cases (25.7%), an uncertain potential hemorrhagic lesion (P1) in 29 cases (41.4%), no potential bleeding lesion (P0) in 2 cases (2.9%), and negative findings (N) in 21 cases (30.0%). In all OGIB, the numbers of blood transfusions > 2 units were found to be significantly associated with findings in the P2 and P1 groups (OR, 3.77; 95% CI, 1.29 - 11.01, $p = 0.013$). In the overt OGIB group, the factor related to a positive finding in CE was age > 55 years (OR, 5.75; 95% CI, 1.12 - 29.41, $p = 0.041$).

Conclusions: Blood transfusion > 2 units in OGIB patients was associated with a positive finding of CE. Age > 55 years was another factor that correlated with a significant positive finding by CE.

Key words: Capsule endoscopy, obscure GI bleeding, OGIB

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB), defined as recurrent or persistent bleeding with negative esophagogastroduodenoscopy (EGD), ileocolonoscopy, and small bowel radiography findings is a big challenge to all endoscopists. OGIB is further classified as overt OGIB and occult OGIB[1]. Overt OGIB is defined as recurrent or persistent visible bleeding with negative endoscopic or radiological workups. Occult OGIB, on the other hand, refers to recurrent or persistent iron deficiency anemia or a positive fecal occult blood test (FOBT) without any detectable source of bleeding[1]. OGIB is the case in about 5% of all gastrointestinal bleedings, the most common site being the small intestine. Visualization of the entire small intestine for sources of bleeding remains problematic. Capsule endoscopy (CE) has been developed more than a decade now as a non-invasive method for examining the small bowel[1]. CE is capable of obtaining images from the entire length of the small intestine in most patients and has been accepted as a first-line investigation in OGIB[1,3]. Recent meta-analyses showed that CE had the highest diagnostic yield for OGIB (61-63%)[4,5], and was comparable to double-balloon enteroscopy (57% and 60%)[6], but much higher than push enteroscopy (28%) and small bowel radiography (8%)[4]. The most common cause of OGIB detected by CE in most studies was angiodysplasia[7,8]. CE was shown to have facilitated early detection of OGIB, potentially improved patient outcomes and reduced resource utilization by obviating the need to repeat endoscopic procedures, hospitalizations, and transfusions[9].

The efficacy of CE in the evaluation of iron deficiency anemia without visible bleeding is still debated[10,11]. Data on CE in OGIB in Asia and on the etiology of OGIB is Asians are limited. CE has been employed to exclude GI causes of iron deficiency anemia. As the benefit of CE varies on the indication for important, therefore, to identify clinical factors for which CE is likely of benefit[12-14]. We conducted this study to identify clinical factors related to positive findings of CE in overt and occult obscure GI bleeding in a Thai population.

MATERIAL AND METHODS

Patients

A retrospective review was made of consecutive patients aged ≥ 15 years with OGIB who underwent CE at Endoscopy unit, Ramathibodi Hospital, between January 2009 and December 2015. OGIB was defined as overt bleeding (hematemesis, hematochezia, or melena) or occult bleeding (positive fecal occult blood test (FOBT), iron deficiency anemia, or an acute drop in hemoglobin) in a patient with unidentified causes from conventional endoscopies (EGD, colonoscopy, or any device-assisted enteroscopy excluding intraoperative enteroscopy). Patients were excluded if they had findings on conventional endoscopy that could explain the bleeding (e.g. Cameron erosions, hemorrhoids). Also excluded were cases with failure of the capsule to enter the small bowel, or small bowel transit time < 1 hour as well as poor visualization of the small intestine. Patients had contraindications for CE, such as pregnancy, known stricture or fistula of the small intestine, inability to swallow, or pressure of equipment of electromedical devices in the body. A written informed consent was obtained from all participants prior to the examination. The study protocol was approved by the Ethical Committee, Ramathibodi Hospital, and the study was conducted in accordance with the Helsinki Declaration.

Capsule endoscopy (CE)

CE studies (PillCam®, Given Imaging, Israel) were performed according to standard protocol, which included an overnight fast and the use of bowel preparation (2 sachets of polyethylene glycol in 2 L of fluid). A realtime monitor technique was periodicity performed to check the position of the capsule[15]. All videos were reviewed by 2 experienced readers, one of whom (PK) had previously reviewed more than 500 cases of CE.

CE findings

CE findings were classified as 4 categories[16]: N; Negative finding, P0; no potential for bleeding (visible submucosal veins, diverticula without presence of blood, or nodules without mucosal break), P1; uncertain hemorrhagic potential (red spots on intestinal mucosa, or small or isolated erosions), P2; high potential of bleeding (typical angiomata, large ulcerations tumors, or varices).

Statistical analysis

Descriptive analysis was used. The results in continuous data were expressed as mean ± SD or median

(min, max). Categorical data were shown as number (percentages). The comparison of numerical variables between groups was accomplished by using the student's *t*-test or the Mann-Whitney test, as appropriate. For comparison of percentages, the Chi-square test or the Fisher's exact test were used for calculation of the odds ratio and 95% CI. Univariate logistic regression of association between findings on CE and selected characteristics (e.g. age group, sex, and underlying disease) was made for significant findings. The value of $p < 0.05$ was considered significant. The SPSS 17.0 for windows was used for statistical analysis.

Results

Between January 2009 and December 2015, 102 CEs were studied, 70 being performed for the indication of OGIB. Patient characteristics were shown in Table 1. There were 26 males (37.1%) and 44 females (62.9%). The mean age of patients with OGIB was 63.4 years (SD 16.3). Thirty seven patients (52.9%) presented with overt OGIB. Among those classified as occult bleeders, 21 (63.6%) had iron deficiency anemia, 2 (9.1%) with fecal occult blood positivity, and 9 (27.3%) had precipitous drop in hemoglobin with a presumed gastrointestinal source. The median number

Table 1. Demographic and baseline clinical characteristic.

	Overt OGIB (n=37)	Obscure OGIB (n=33)	*p*-value
Age yr†	59.1 ± 16.63	61.6 ± 16.17	0.522
Sex Female	18 (48.6)	26 (78.8)	0.009
Underlying disease			
DM (n, %)	8 (21.6)	9 (27.2)	0.621
HT (n, %)	12 (32.2)	9 (27.3)	0.532
CAD (n, %)	4 (11.4)	7 (21.2)	0.274
VHD (n, %)	5 (13.5)	2 (6.3)	0.431
AF (n, %)	2 (5.4)	2 (6.1)	1.000
CKD (n, %)	6 (16.2)	1 (3)	0.107
Cirrhosis (n, %)	3 (8.1)	1 (3)	0.614
Old CVA (n, %)	2 (13.5)	0	0.493
Autoimmune disease (N, %)	1 (2.7)	0	1.000
Infection (n, %)	3 (8.1)	1 (3)	0.614
Malignancy (n, %)	6 (16.2)	1 (3)	0.107
Drug			
Antiplatelet (n, %)	7 (18.9)	6 (18.2)	1.000
Warfarin (n, %)	5 (13.5)	3 (9.1)	0.714
NSAIDS (n, %)	7 (18.9)	5 (15.2)	0.758
Laboratory			
Hb†	7.885 ± 2.47	9.160 ± 2.20	0.031
Change Hb†	3.7 (0.6,8.9)	1.9 (0.2,5.9)	0.004
Platelet†	214128.62 ± 102823.84	295320.02 ± 109422.62	0.008
WBC†	7981.81 ± 3710.01	6828.82 ± 2534.21	0.198
INR‡	1.07 (0.89,22.70)	1.94 (0.97,3.48)	0.085
BUN‡	15.5 (6,64)	18 (13,35)	0.870
Cr‡	1.05 (0.7,10.9)	0.79 (0.5,1.6)	0.149
Episode GI bleed‡	1.00 (1.0,1.0)	0	0.000
No. of transfusions‡	3.00 (2.0, 5.0)	0	0.000
Number EGD‡	1.00 (1.0, 5.0)	1.00 (1.0, 2.0)	0.082
Number Colonoscopy‡	1.00 (1.0, 2.0)	1.00 (1.0, 2.0)	0.439
Time to capsule (day)‡	9.50 (6.0,33.5)	-	-

†mean ± SD

‡median (min, max)

Table 2. Capsule result.

Capsule result	Overt OGIB (n=37)	Obscure OGIB (n=33)	Total (n=70)
N	10 (27.0)	11 (33.3)	21 (30.0)
P0 (%)	0	2 (6.1)	2 (2.9)
P1 (%)	13 (35.1)	16 (48.5)	29 (41.4)
P2 (%)	14 (37.8)	4 (12.1)	18 (25.7)
Etiologies			
Angiodysplasia (%)	8 (21.6)	1 (3)	9 (12.9)
Erythematous spots (%)	7 (18.9)	5 (15.2)	12 (17.1)
Erosions (%)	3 (8.1)	9 (27.3)	12 (17.1)
Ulcer (%)	3 (8.1)	2 (6.1)	5 (7.1)
Tumor (%)	3 (8.1)	2 (6.1)	5 (7.1)
Meckel diverticulum (%)	1 (2.7)	0	1 (1.4)
Active bleeding (%)	2 (5.4)	0	2 (2.9)

Table 3. Obscure GI bleeding.

	Group1 [P1, P2 (n=47)]	Group2 [P0, N (n=23)]	*p*-value
Age Yr†	62.70 ± 15.88	55.39 ± 16.53	0.079
Sex Female (N, %)	28 (59.6)	16 (69.6)	0.445
Underlying disease			
DM (N, %)	11 (23.4)	6 (26.1)	1.000
HT (N, %)	13 (27.7)	8 (34.8)	0.782
CAD (N, %)	7 (14.9)	4 (17.4)	1.000
VHD (N, %)	7 (14.9)	0	0.086
AF (N, %)	4 (8.5)	0	0.292
CKD (N, %)	5 (10.6)	2 (8.7)	1.000
Cirrhosis (N, %)	3 (6.4)	1 (4.3)	1.000
Old CVA (N, %)	2 (4.3)	0	0.546
Autoimmune disease (N, %)	0	1 (4.3)	0.338
Infection (N, %)	3 (6.4)	1 (4.3)	1.000
Malignancy (N, %)	6 (12.8)	1 (4.3)	0.409
Drug			
Antiplatelet (N, %)	10 (21.3)	3 (13.0)	0.523
Warfarin (N, %)	6 (12.8)	2 (8.7)	0.712
NSAIDs (N, %)	9 (19.1)	3 (13.0)	0.738
Laboratory			
Hb†	11.57 ± 1.54	11.66 ± 1.16	0.389
Change Hb‡	3 (0.2, 8.9)	2.3 (0.3, 7.7)	0.309
Platelet†	242974.36 ± 109294.99	278757.14 ± 121772.90	0.313
WBC†	7152.56 ± 2812.82	8232.86 ± 4212.14	0.288
INR‡	1.09 (0.89, 22.7)	1.07 (1.03, 1.87)	0.628
BUN‡	21 (10, 64)	14 (6, 19)	0.112
Cr‡	0.84 (0.47, 10.9)	0.98 (0.51, 1.48)	0.815
Episode GI bleed‡	0 (0,3)	0 (0,4)	0.994
No. of transfusions‡	2 (0,10)	0 (0,9)	0.022
< 2 (%)	17 (37.8)	16 (69.6)	0.013
≥ 2 (%)	28 (62.2)	7 (30.4)	
Number of EGD‡	1.00 (1.0,3.0)	1.00 (1.0,5.0)	0.934
Number of Colonoscopy‡	1.00 (1.0,2.0)	1.00 (1.0,1.0)	0.979

†mean ± SD; ‡median (min, max)
group 1 = P2, P1 lesion; group 2 = P0, N lesion

of EGDs received before CE was 1[(1,5)], and the median number of colonoscopies was 1[(1,2)]. Diabetes mellitus, hypertension, and coronary artery disease were common comorbid diseases in our patients. As for medications, no significant differences were noted between the overt OGIB group and the occult OGIB group regarding ingestion of antiplatelet agent, anticoagulation, and NSAIDs. As for blood chemistry, changes of hemoglobin levels were higher in the overt OGIB group, whereas was hemoglobin level and the platelet level were significantly higher in the occult OGIB group. An episode of bleeding was found only in the overt OGIB and the number of blood transfusion was significantly higher in the overt OGIB.

For endoscopic findings, erosions and erythematous spots were the most common lesions (17.1% each), followed by angiodysplasia (12.9%), ulcers (7.1%), and tumors (7.1%) (Table 2). Categorized by capsule finding results, high potential bleeding lesions (P2) were noted in 18 cases (25.7%), uncertain potential hemorrhagic lesions (P1) in 29 cases (41.4%), no potential bleeding lesions (P0) in 2 cases (2.9%), and negative findings (N) 21 cases (30%). Small bowel enteroscopy was performed in 8 cases (overt OGIB 7, occult OGIB 1). Long GI study was performed in 1 case (overt OGIB). Computer tomography of the whole abdomen

Table 4. Overt GI obscure GI bleeding.

	Group 1 [P1, P2 (n=27)]	**Group 2 [P0, N (n=10)]**	***p*-value**
Age yr†	62.41 ± 15.47	50.18 ± 17.45	0.044
< 55 (%)	4 (14.8)	5 (50)	
> 55 (%)	23 (85.2)	5 (50)	0.041
Sex Female (n, %)	13 (48.1)	5 (50)	1.000
Underlying disease			
DM (n, %)	5 (18.5)	3 (30)	0.661
HT (n, %)	8 (29.6)	4 (40)	0.706
CAD (n, %)	3 (11.1)	1 (10)	1.000
VHD (n, %)	5 (18.5)	0	0.292
AF (n, %)	2 (7.4)	0	0.580
CKD (n, %)	4 (14.8)	2 (20)	1.000
Cirrhosis (n, %)	2 (7.4)	1 (10)	1.000
Old CVA (n, %)	2 (7.4)	0	0.580
Autoimmune disease (n, %)	0	1 (10)	0.286
Infection (n, %)	2 (7.4)	1 (10)	1.000
Malignancy (n, %)	6 (22.2)	0	0.152
Drug			
Antiplatelet (n, %)	5 (18.5)	2 (20)	1.000
Warfarin (n, %)	3 (11.1)	2 (20)	0.597
NSAIDs (n, %)	5 (18.5)	2 (20)	1.000
Laboratory			
Hb†	11.66 ± 1.79	11.73 1.35	0.910
Change Hb‡	4 (0.6, 8.9)	3.05 (1, 7.7)	0.634
Platelet†	198523.81 ± 104757.63	260942.86 ± 87106.96	0.168
WBC†	7141.43 ± 2952.89	10502.86 ± 4794.47	0.121
INR‡	1.07 (0.89, 0.27)	1.08 (1.03, 1.87)	1.000
BUN‡	23 (10, 64)	10 (6, 14)	0.051
Cr‡	1.34 (0.74, 10.9)	0.91 (0.83, 1.05)	0.540
Episode GI bleed‡	1 (1, 3)	1 (1, 4)	0.089
No. of transfusions‡	3 (0, 10)	1 (0, 9)	0.310
Number of EGD‡	1 (1, 3)	1 (1, 5)	0.814
Number of Colonoscopy‡	1 (1, 2)	1 (1, 2)	0.868

†mean ± SD; ‡median (min, max)
group 1 = P2, P1 lesion; group 2 = P0, N lesion

was performed in 2 cases (overt OGIB 1, occult OGIB 1). Partial small bowel resection was performed in 5 cases (overt OGIB 3, occult OGIB 2). Procedure related complications were noted in 1 case (failure of CE to reach the cecum due to an identified pathology), and capsule retention due to mass lesion was encountered in 2 cases (overt OGIB 1, occult OGIB 1).

The number of blood transfusion > 2 units was the only significantly factor between the two groups ($p = 0.013$). The number of endoscopies such as EGD and colonoscopy was not different between the two groups.

By categorization as overt OGIB or occult OGIB, only age > 55 years was significantly different between group 1 (P1, P2 lesion) and group 2 (P0, N lesion) ($p = 0.041$) (Table 4). The median of the number of blood transfusion units was higher in group 1 than group 2, without statistical significance. The positive yield of CE was higher in patients with evidence of bleeding within 14 days of CE compared to those who had remote overt bleeding (> 14 days of CE), but without statistical significance ($p = 0.687$) (Table 5). In the occult OGIB group, there was difference in the number of transfusions between group 1 and group 2 ($p = 0.047$) For the univariate logistic regression analysis, we found that receiving blood transfusion > 2 units in overt OGIB patients was associated with a positive finding of CE in OGIB ($p = 0.013$), and age > 55 years was another factor that was related to a significant positive finding by CE in overt OGIB ($p = 0.041$) (Table 6).

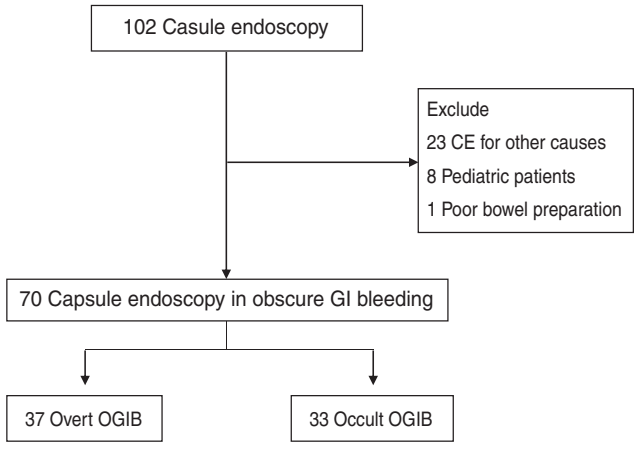

Figure 1. Study flow chart.

Table 5. Time to capsule endoscopy.

Days	Group 1 (n=73)	Group 2 (n=10)	*p*-value
< 7	10 (37%)	2 (20%)	0.416
8-14	8 (29.6%)	3 (30%)	
14-30	4 (14.8%)	2 (20%)	
>30	5 (18.5%)	3 (30%)	

Days	Group 1 (n=73)	Group 2 (n=10)	*p*-value
< 14	18 (66.7%)	5 (50%)	0.687
> 14	9 (33.3%)	5 (50%)	

group 1 = P2, P1 lesion
group 2 = P0, N lesion

Table 6. Univariate Logistic Regression of Association Between Findings on CE group (P2, P1 vs P0, N) and Selected Characteristics.

Characteristic	OR	95% CI	*p*-value
Obscure GI bleeding			
No. of transfusions ≥ 2	3.77	1.29-11.01	0.013
Overt GI obscure GI bleeding			
Age (yr) ≥ 55	5.75	1.12-29.41	0.027

DISCUSSION

Current guidelines have suggested algorithms to identify a causative pathology of OGIB, which strongly rely on the nature of the presenting symptoms. Unfortunately, most current tests are costly, and inappropriate diagnostic selection can lead to a delayed diagnosis, resulting in increased financial demands and poor patient outcomes. This brings in the identification of clinical and demographic factors that can help appropriate diagnostic selection. A number of studies have attempted to identify predictors of positive pathology on CE in OGIB[7,17-20]. The largest cohort to date to assess the correlation of clinical and demographic factors with positive findings on CE found that the significant factors associated with positive findings were the increasing number of EGDs before CE, the number transfusion requirements, and the presence of comorbid CTD[7]. Another study showed that the timing of CE studies within 48 hours of an episode of overt bleed was a significant factor[20].

In our series of patients with OGIB, capsule en-

Table 7. Occult obscure GI bleeding.

	(n=20)	(n=13)	*p*-value
Age yr†	63.1 ± 16.9	59.4 ± 15.2	0.540
Sex Female (n, %)	15 (75.0)	11 (84.6)	0.676
Underlying disease			
DM (n, %)	6 (31.6)	3 (23.1)	0.704
HT (n, %)	5 (25.0)	4 (30.8)	1.000
CAD (n, %)	4 (20.0)	3 (23.1)	1.000
VHD (n, %)	2 (10.0)	0	0.516
AF (n, %)	2 (10.0)	0	0.508
CKD (n, %)	1 (5.0)	0	1.000
Cirrhosis (n, %)	1 (5.0)	0	1.000
Old CVA (n, %)	0	0	
Autoimmune disease (n, %)	0	0	
Infection (n, %)	1 (5.0)	0	1.000
Malignancy (n, %)	0	1 (7.7)	
0.394			
Drug			
Antiplatelet (n, %)	5 (25.0)	1 (7.7)	0.364
Warfarin (n, %)	3 (15.0)	0	0.261
NSAIDs (n, %)	4 (20.0)	1 (7.7)	0.625
Laboratory			
Hb†	11.4 ± 1.16	11.6 ± 1.06	0.701
Change Hb‡	2 (0.2, 5.9)	1.7 (0.3, 5)	0.734
Platelet†	294833.33 ± 92208.36	296571.43 ± 154274.49	0.972
WBC†	7165.56 ± 2725.24	5962.86 + 1852.30	0.296
INR‡	1.94 (0.97, 3.48)	-	-
BUN‡	17 (13, 35)	18 (17, 19)	1.000
Cr‡	0.74 (0.47, 1.64)	1.2 (0.51, 1.48)	0.909
No. of transfusions‡	0 (0, 4)	0 (0, 2)	0.047
< 2 (%)	13 (65)	12(92.3)	0.108
≥ 2 (%)	7 (35)	1 (7.7)	
Number of EGD‡	1 (1, 2)	1 (1, 2)	0.814
Number of Colonoscopy‡	1 (1, 2)	1 (1, 2)	0.868

†mean ± SD; ‡median (min, max)
group 1 = P2, P1 lesion; group 2 = P0, N lesion

doscopy was well-tolerated and helpful in directing further diagnostic and therapeutic strategy. The demographic characteristics of patients in this series were representative of patients in a tertiary care center for OGIB. Patients had previously undergone several tests, procedures, and hospitalizations due to GI bleeding. It was not possible to predict the effect of the use of medications such as warfarin, aspirin, or other NSAIDs in the multivariate analysis because of the small sample size. However, the amount of blood transfusions >2 unit was found to be significantly associated with a positive finding of CE. Other common endoscopic findings such as erosions, erythematous spots, and angiodysplasia were not different from those in previous studies.

The correlation between the timing and the yield of CE remains a controversial issue. One study[7] found the highest yield in patients with ongoing GI bleeding, and therefore argued for ordering CE earlier in the setting of overt OGIB. In our patients, group 1 (P2 and P1) lesions could be detected in 72.9 % of patients with overt OGIB, compared to 60.6 % in patients with oc-

cult OGIB. Moreover, the diagnostic yield of CE was higher in patients who had evidence of bleeding within 14 days of CE, compared to those who had a remote overt bleeding (> 14 days of CE), but without statistical significant (p= 0.687).

The median time interval of CE after the onset of OGIB in the present study was 9.5 days (range 6-33.5 days). As the range of time interval was rather wide, later performances of CE in our study might have under detected small bowel ulcers or other NSAIDs-related lesions, as suggested by a recent study[21].

The major complication noted during CE was capsule retention, usually in the small intestine, necessitating endoscopic or surgical removal. Published rates of this complication range from 0.75-5%[7,22]. Capsule retention was 2.9% in our study.

The current study had several limitations. Firstly, it was a retrospective single-center study. Data collection bias could have occurred. Secondly, our sample size was small, such that certain significant findings by CE might not reach a statistical significance. Thirdly, the time between capsule and the study could have been inaccurate due to retrospective bias.

In conclusion, receiving blood transfusion > 2 units in overt OGIB patients were associated with a positive finding of CE in OGIB. Age > 55 years was another significantly positive factor in overt OGIB.

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