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Abstract

AIM: To assess the clinical impact of capsule endoscopy (CE) in the long-term follow-up period in patients with obscure gastrointestinal bleeding (OGIB).

METHODS: One hundred and forty-one patients who applied CE for OGIB between 2009 and 2012 were retrospectively analyzed, and this cohort was then questioned prospectively. Demographic data of the patients were determined via the presence of comorbid diseases, use of non-steroidal anti-inflammatory drugs, anticoagulant-antiaggregant agents, previous diagnostic tests for bleeding episodes, CE findings, laboratory tests and outcomes.

RESULTS: CE was performed on 141 patients because...
INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages[1-3]. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB[4-6]. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks. In this study, our main aim was to determine the long-term clinical impact of capsule endoscopy during follow-up period.

MATERIALS AND METHODS

Patients

The data obtained from the patients presented to gastroenterology department and referred to endoscopy unit with OGIB from January 2009 to December 2012 was analyzed in a retrospective design. This cohort was then questioned prospectively.

Before the CE procedure, all of the patients were applied colonoscopy and upper GI endoscopy (GIE) in our endoscopy unit. The collected data from the patients included their demographics, previous intake of anticoagulant/antiaggregant therapy, non-steroidal anti-inflammatory drugs (NSAIDs), present comorbidities, their previous diagnostic test results (upper GIE, colonoscopy, radiological studies of small bowel, computerized tomography (CT) imaging), CE findings and follow-up data.

Before the CE procedure, the passage opening was evaluated using CT. CE was not undertaken in patients who had strictures or obstructions.

The study was done after the patients were informed about this study and the patients’ written informed consents were taken according to Helsinki Declaration. The study was obtained from local ethics committee.

CE procedure

CE procedures were performed on an outpatient basis without hospitalization. Pillcam SB2 (Given Imaging, Yoqneam, Israel) was used for the procedure. Patients’ bowel preparation was done using 4 L polyethylene glycol solution one day before the procedure. The patients swallowed the capsules (Pillcam SB2) in the outpatient clinic. Fluid intake was permitted 2 h and eating was allowed 4 h after the initial administration of capsules. Patients were instructed to check their stool for the ejection of capsule and to notify the endoscopy unit if it was not ejected. Failure of the capsule ejection in more than 2 wk was defined as capsule retention in the GI tract. One gastroenterologist (F-A) with extensive experience in small bowel endoscopy evaluated the recorded CE images.

Follow-up

Charts were used to gather full follow-up information including OGIB recurrence and CE complications. Each patient was called and reevaluated for the follow-up period. Overt bleeding or the decrease in Hb levels >
2 g/dL were considered as "rebleeding".

**Statistical analysis**

Statistical analysis was performed using Number Cruncher Statistical System 2007 with Power Analysis and Sample Size 2008 statistical software. The data was analyzed by definitive methods (mean, standard deviation, median, minimum, maximum, frequency, ratio,) together with Pearson's χ² test, Fisher-Freeman-Halton test, Yates's Continuity Correction test. In the determination of multivariate effects of the variables on rebleeding, Stepwise logistic regression analysis was used. Significance levels were determined as P < 0.01 and P < 0.05.

**RESULTS**

CE was performed on 141 patients with OGIB. The capsule was retained in the upper GI tract in two patients thus video monitoring was not achieved. The first patient was diagnosed as having achalasia after CE, and the second had gastric diabetic gastroparesis by further investigation. A total of 139 patients (62% male) who applied CE had available follow-up data. Median age of patients was 72 years (13-93) and median follow-up duration was 32 mo (6-82 mo). In 112 of the 139 (80.6%) patients, capsule transit time to caecum was within the recording time. Spontaneous elimination of the capsule within 2 wk was seen in 133 (95.4%) patients. Capsule retention was found in 6 patients (4.6%). The overt obscure bleeding rate was 61.9% (n = 86), whereas the rate for occult obscure bleeding was 38.1% (n = 53). Comorbidities were detected in 35.5% (n = 50) of the patients. NSAIDs, anticoagulant-antiaggregant drugs were used at a rate of 18.9% (n = 26). CE was positive in 118 (84.9%) patients (Table 1).

**Long-term outcome of CE**

Rebleeding was seen in 40.3% of the patients (26.4% occult and 48.8% overt bleeding, P = 0.015). The rebleeding rate was 46.6% (55/118) in patients with positive CE and 4.8% (1/21) with negative CE results at the end of follow-up period. Evaluation of rebleeding in relation with the demographic data is shown in Table 2. Both univariate and multivariate analyses were performed to find out the factors related with a higher risk of rebleeding. When we evaluated the effects of comorbidity, age, overt presentation, NSAIDs-anticoagulant-antiaggregant therapy and vascular lesion on rebleeding by stepwise logistic regression analysis, the OR for the effect of NSAIDs-anticoagulant-antiaggregant therapy on rebleeding was 5.8 (95%CI: 1.86-18.27), and 6.027 (95%CI: 2.56-14.14) for vascular lesions. Although, OR was 2.274 (95%CI: 0.86-5.98) for comorbidities, it was not statistically significant. The association analysis is detailed in Table 3. One patient who had diverticulosis coli and negative CE died because of bleeding at 46 mo. The specificity of the CE was found to be 95.2% and positive predictive value was 98.2% in the prediction of rebleeding. Treatment was applied to 29 patients (51.7%): Surgery (n = 4), argon plasma coagulation (n = 11), transcatheter aortic valve implantation (TAVI) (the reason of the bleeding was aortic stenosis so to treat that TAVI procedure was applied) (n = 2), hormonal therapy (n = 2), reason based treatment (NSAIDs, anticoagulant, antiplatelet, antiaggregant drugs withdrawal) (n = 10). Seven patients died at the end of the follow-up and six of them died because of a rebleeding episode.

**DISCUSSION**

For the diagnosis of OGIB, capsule endoscopy is a useful imaging technique. Therefore, it is accepted as a gold standard method and should be the first step in the management of patients with OGIB[7]. The number of studies about the results of CE in long-term is limited[6-10]. In this study, we assessed the impact of CE in the long-term period (median: 32 mo) in patients with OGIB. The diagnostic yield of CE was 84.9%. Rebleeding was determined in 40.3% (56/139) in patients with OGIB. Specificity of CE was 95.2% and positive predictive value for rebleeding was 98.2%. Previous studies in the

| Table 1 | Capsule endoscopy findings in patients with obscure gastrointestinal bleeding |
|---------|--------------------------------|
| Findings                              | n (%) |
| Positive findings in CE               | 118 (84.9) |
| Normal                                | 21 (15.1) |
| Angiodysplasia                        | 27 (19.42) |
| Polyloid lesion                       | 25 (17.98) |
| Uler                                  | 25 (17.98) |
| Erosions                              | 22 (15.82) |
| Malign lesions                        | 7 (5.12) |
| Active bleeding                       | 4 (2.87) |
| Portal hypertensive enteropathy       | 2 (1.43) |
| Mucosal bleeding                      | 2 (1.43) |
| Arteriovenous malformation            | 2 (1.43) |
| Diverticulum                          | 1 (0.71) |
| Parasite infection                    | 1 (0.71) |

CE: Capsule endoscopy.

| Table 2 | Evaluation of rebleeding according to the demographic data n (%) |
|---------|---------------------------------------------------------------|
| Rebleeding |                | P |
| (+)       | (-)             |   |
| Age, n (%) |                |   |
| < 70 yr    | 32 (32)         | 68 (68) | 0.015 |
| > 70 yr    | 24 (61.5)       | 15 (38.5) | 0.001 |
| Comorbidity |                |   |
| Positive capsule result               | 55 (46.6) | 63 (53.4) | 0.001 |
| NSAIADs-antiagulant-anitaggren therapy | 19 (73.1) | 7 (26.9) | 0.001 |

ns: Pearson Chi-Square test; *P < 0.05, **P < 0.01. OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs.
Table 3 Risk factors for rebleeding (univariate-multivariate analysis)

| Univariate | Multivariate |
|------------|-------------|
|            | OR 95%CI    | P     | OR 95%CI    | P     |
| Comorbidity| 5.176 2.442-10.972 | 0.001a | 2.274 0.864-5.986 | 0.096 |
| Age        | 3.400 1.574-7.342 | 0.001a | 1.735 0.595-5.057 | 0.313 |
| Overt OGIB | 2.659 1.265-5.589 | 0.015a | 1.222 0.490-3.048 | 0.667 |
| NSAIDs-anticoagulant-antiagregant therapy | 5.575 2.153-14.438 | 0.001a | 5.843 1.868-18.275 | 0.002a |
| Vascular lesion | 6.438 2.852-14.625 | 0.001a | 6.027 2.568-14.146 | 0.001 |
| Positive CE results | 17.460 2.269-134.371 | 0.001a | - - | - |

*a P < 0.05; **P < 0.01. OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs; CE: Capsule endoscopy.

Table 4 Rebleeding rates in different studies

| Ref. | Total number of case | Follow-up duration (mo) | Rebleeding rates after negative CE (%) |
|------|----------------------|------------------------|---------------------------------------|
| Lai et al [11] | 49 | 12 | 6 |
| MacDonald et al [12] | 49 | 17 | 11 |
| Park et al [13] | 51 | 32 | 36 |
| Delvaux et al [14] | 44 | 12 | 0 |
| Iwamoto et al [15] | 78 | 6 | 4 |
| Lorenceau-Savale et al [16] | 35 | 12 | 0 |
| Koh et al [17] | 51 | 23 | 25 |

CE: Capsule endoscopy.

The literature reported lower bleeding ratios in patients with negative CE results in comparison with positive [11-13]. Delvaux et al.'s study on 44 patients in one-year follow-up period reported that the negative predictive values were 100% in patients with negative CE and the positive predictive values of CE were 94.4% in patients with positive CE results. Arakawa et al.'s also reported that none of their patients who had a normal CE had rebleeding. As compatible with the literature, only one patient has a rebleed who had a normal CE in our group. The follow-up time is important for patients who have negative CE. In our study, the mean follow-up duration for patients was 46 ± 21 mo (range: 6-82 mo). The rebleeding rate is variable in the literature (0%-36%, Table 4) [11-14,16-18]. However, the main restriction of these studies is the small group of patients and their relatively short follow-up periods. Rahmi et al.'s showed that overt OGIB at presentation was a risk factor for rebleeding. We also found that the rebleeding ratio was higher in overt obscure bleeding when compared with occult obscure bleeding (48.8% vs 26.4%, P = 0.015). Vascular lesions were more susceptible to rebleeding when it was compared with the others (72.1% vs 27.9%, P = 0.001). These results also confirm the results of previous studies [19,21]. In present study, NSAIDs-anticoagulant-antiagregant therapy (OR = 5.8; 95%CI: 1.86-18.27) and vascular ectasia (OR = 6.02; 95%CI: 2.568-14.146) were detected as an independent risk factors for rebleeding in the multivariate analysis. In univariate analysis; advanced age, comorbidity, overt bleeding, were also detected as a predictors of rebleeding. Therefore, anticoagulant/antiagregant/NSAIDs users, and vascular lesions in CE should be follow-up carefully because of the high rebleeding rate. Our long-term follow-up results were compatible with the short-term follow-up results in the literature [20-23].

In conclusion, CE is a reliable method in the diagnosis of obscure GI bleeding. Negative CE correlated with a significantly lower rebleeding risk in the long-term follow-up period.

COMMENTS

Background
Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks.

Research frontiers
Diagnosis of OGIB is mostly dependent on CE. However, there is not enough data about the long-term outcomes of patients with OGIB who applied CE.

Innovations and breakthroughs
The authors evaluated 139 patients with OGIB diagnosed by CE in a long-term follow-up study. Several risk factors for rebleeding were detected. Negative CE correlated with a significantly lower rebleeding rate.

Applications
CE is a safe, well-tolerated and powerful diagnostic tool which may also provide prognostic implications.

Terminology
OGIB usually originates from small bowel and is not detected by both endoscopy.
It is an important novel study on CE for diagnosis of obscure GI bleeding and rebleeding rates on long term basis.

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