Prospective Evaluation of Gastrointestinal Lesions by Bidirectional Endoscopy in Patients with Iron Deficiency Anemia

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Background: *Occult bleeding from the gastrointestinal (GI) lesions is a common cause of iron deficiency anemia (IDA). The information concerning the prevalence and the appropriate strategy for evaluation of IDA in Thai patients is scanty.*
Objective: *Prospectively evaluate Thai patients with IDA for GI lesions using bidirectional endoscopy.*
Material and Method: *Consecutive patients with IDA were investigated by esophagogastroduodenoscopy (EGD) and colonoscopy. Significant GI lesions were identified. Clinical data and results of the fecal occult blood testing (FOBT) were collected to determine factors associated with the presence of GI lesions.*
Results: *One hundred three patients were included in this study and the mean age was 63.6 $\pm$ 15.2 years old. Significant GI lesions were detected in 58 patients (56%), 43% by EGD, 25% by colonoscopy. Twelve patients (12%) had dual lesions identified from both EGD and colonoscopy. The most common lesions were peptic ulcers (22%) and colonic carcinoma (13%). Anti-platelets use and positive FOBT were associated with the significant GI lesions with odds ratios of 2.37 (95% CI 1.05-5.36, p = 0.036) and 2.83 (95% CI 1.05-7.68, p = 0.038), respectively. FOBT had sensitivity, specificity, positive predictive value, and negative predictive value for significant GI lesions at 81%, 40%, 68%, and 66%, respectively. Site-specific symptoms correctly guided the route of endoscopy in 60-80% of the patients.*
Conclusion: *EGD resulted in a better yield than colonoscopy and was the preferred route of initial endoscopy unless there was suggestive site-specific symptom. Bidirectional endoscopy was finally required in most patients unless a cancerous lesion was detected by the initial endoscopy.*

Keywords: *Iron deficiency anemia, Bidirectional endoscopy, Esophagogastroduodenoscopy, Colonoscopy, Fecal occult blood test*

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Iron deficiency anemia (IDA) is an important health problem worldwide. In patients without obvious causes of blood loss, gastrointestinal (GI) tract is found to be the most common site of occult blood loss and the etiology varies from benign to malignant lesions. Therefore, the standard work-up strategy for patients with IDA is the evaluation of the GI tract for GI lesions. The British Society of Gastroenterology guideline[1] and the American Gastroenterology Association guideline[2] advocated both esophagogastroduodenoscopy (EGD) and colonoscopy based on evidences from many studies, which had shown that EGD could detect lesions in 28-56% (average 38%), colonoscopy in 14-30% (average 24%) and bidirectional endoscopy detected dual lesions in 0-29% (average 10%)[3-8]. However, there are still controversies to such approaches.

The sequence of route of endoscopy is a matter of much debate. Some suggested using GI symptoms as a guide for determining the initial route of endoscopy[6], whereas others and most guidelines concluded that symptoms were not good predictors[1,2,5]. In the absence of site-specific symptoms, some advised starting with colonoscopy[2], while others preferred EGD[1].

In Thailand, two studies have investigated on the causes of GI tract blood loss in patients with IDA. Ovartlarnporn[9] investigated 44 Thai IDA patients using EGD and barium enema. GI lesions were detected in 50% of cases. In other study by Sophonthanasiri[10]

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using bidirectional endoscopy detected GI lesions in only 17% of 69 IDA patients. Such discrepancy of results may reflect the differences of criteria of case inclusion and the variation of definitions of GI lesions considered as causes of IDA. Meanwhile, although most guidelines concluded that guaiac-based fecal occult blood test (FOBT) was neither sensitive nor specific for predicting GI lesions, it remained the common resorted test among general practitioners in the work-up of IDA. Whether the FOBT is helpful in predicting GI lesions or deciding which route of initial endoscopy in Thai patients with IDA is unknown.

The aims of the present study were to elucidate the prevalence, the sites and types of GI lesions identified by bidirectional endoscopy as the causes of IDA in Thai patients and to identify variables or factors (including the FOBT) that may help predict the presence of GI lesions, as well as indicate the appropriate initial route of endoscopy for the work-up of IDA.

Material and Method

Study population

All outpatients with IDA who were referred to the Gastroenterology Division at Siriraj Hospital between October 2007 and October 2008 were prospectively enrolled into the present study. IDA was defined as a hemoglobin concentration $\leq$ 13 g/dl for men and $\leq$ 12 g/dl for women, accompanied by at least one of the following laboratory findings which were consistent with IDA: a serum iron $\leq$ 45 μg/dl with a transferrin saturation $\leq$ 15%, a serum ferritin concentration $\leq$ 20 μg/l for men and $\leq$ 10 μg/l for women, peripheral blood smear revealed hypochromic microcytic red cells with normal hemoglobin typing, anemia responded to iron supplement *i.e.*, increased hemoglobin level at least 1 g/dl per week. Exclusion criteria were an obvious cause of blood loss within three months, hypermenorrhea, vegetarian, history of gastrectomy, concurrent diagnosis of GI cancer, chronic kidney disease, pregnancy, patients with thrombocytopenia ($< 50{,}000/mm^3$), age under 18 years old, and inability to give informed consent for endoscopy.

Based on the above criteria, 103 consecutive patients were enrolled into the present study. They were advised for the complete evaluation of the upper and lower GI tract irrespective of the presence of GI symptoms. Informed consent was obtained from all patients.

Data collection

Clinical data

Before the endoscopic procedures, patients were clinically evaluated by gastroenterology fellows at the time of patient's presentation. A detailed structured questionnaire which included age, sex, presence of upper GI symptoms (upper abdominal pain, dyspepsia, nausea, vomiting, dysphagia, heartburn, reflux) or lower GI symptoms (lower abdominal pain, change of bowel habit, diarrhea, constipation), use of aspirin and non-steroidal anti-inflammatory drugs, use of alcohol and/or tobacco within three months before endoscopy, and FOBT (non-rehydrated hemooccult II; Hema-screen, Stanbiolab, Texas) was requested.

Laboratory data

Standard routine blood tests (included CBC, iron study) were obtained in all patients. The results of FOBT were available in 82 patients. The results of all clinical information and laboratory results were recorded systematically.

Endoscopic data

The initial route of endoscopy was chosen according to the patient's symptoms. In the absence of suggestive GI symptoms, EGD was performed first. If significant lesions considered likely to be the cause of IDA were not found, the other route of endoscopy was subsequently performed. In patients older than 50 years old, bidirectional endoscopies were performed in all cases unless the initial endoscopy revealed carcinoma. The definition of significant lesions for EGD was: carcinoma, esophagitis with erosions or ulceration involving > 10% of the distal 5 cm of esophagus, erosive gastritis or duodenitis (defined by at least 50 erosions $\geq$ 1 mm diameter with white bases encircled by erythema), single duodenal or gastric ulcer $\geq$ 1 cm in diameter or two ulcers $\geq$ 0.5 cm in diameter, adenomatous polyp over 1.5 cm in diameter, $\geq$ 5 vascular ectasia or $\geq$ 8 mm in diameter. Significant lesions for colonoscopy were carcinoma, adenomatous polyps over 1.5 cm in diameter, $\geq$ 5 vascular ectasia or $\geq$ 8 mm in diameter, active colitis, and colonic ulcer larger than 1 cm in diameter[6].

Statistical analysis

Statistical analysis was done using SPSS version 13 program. Descriptive statistic was used where appropriate. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for FOBT. Univariate analysis

of the correlation between clinical parameters and significant GI lesions were analyzed. Chi-square test for categorical variable and student t-test for continuous variable data were calculated. Statistical significance was considered when $p < 0.05$.

The present study was approved by the Ethics Committee of Siriraj Hospital.

Results

During the study period, 133 patients were referred to the GI division for the evaluation of IDA. Thirty patients were excluded, 27 did not meet the criteria for IDA and three had incomplete endoscopic evaluation. Therefore, 103 patients were included in the present study.

Baseline information

The baseline information of 103 patients and the numbers and types of endoscopic examination performed are shown in Table 1. Two-third of the patients were female with a mean age of 64 years old. GI symptoms which were present in 39 patients (38%) were dysphagia (1 patient), nausea/vomiting (1 patient), heartburn (1 patient), dyspepsia (12 patients), abdominal pain (6 patients), diarrhea (2 patients), constipation (14 patients), and lower abdominal pain (4 patients).

Endoscopic findings

Significant GI lesions were detected in 58 of the 103 patients (56%). EGD demonstrated significant lesions in 44 patients (43%) whereas colonoscopy demonstrated significant lesions in 26 patients (25%). Dual lesions from both EGD and colonoscopy were identified in 12 patients (12%). Insignificant lesions or normal findings were found in 45 patients (44%) (Table 2).

Details of the endoscopic findings in all patients are shown in Table 3. Peptic ulcer (PU) and colonic carcinoma were the most common lesions detected by EGD (22%) and colonoscopy (13%), respectively. The findings of 12 patients with dual lesions were PU with colonic carcinoma (2 patients), PU with large polyps (2 patients), PU with colonic ulcers (3 patients), PU with vascular ectasia (1 patient), erosive gastritis with large polyps or colonic ulcers (2 patients each).

Predictors of significant GI lesions

Univariate analysis of the possible factors associated with significant GI lesions is presented in Table 4. The use of anti-platelets medications and the positive FOBT were the only two predictors for significant GI lesions (OR 2.37 and 2.83, respectively). However, the sensitivity, specificity, PPV and NPV of FOBT for significant GI lesions were 81%, 40%, 68%, and 66%, respectively. The presence of GI symptoms did not predict the presence of GI lesions.

The site-specific GI symptoms

Twenty-one patients had upper GI symptoms alone and significant lesions were found in 17 (81%). EGD could detect lesions in 14 cases (82%), whereas three (18%) had lesions in the colon. Likewise, eight patients had lower GI symptoms alone and five (63%) had significant GI lesions. However, three (60%) were detected by colonoscopy and two (40%) were detected by EGD.

Sixty-four patients had no GI symptoms. Significant GI lesions were found in 25 patients (39%) by EGD and 11 patients (17%) by colonoscopy.

Discussion

IDA in adults without obvious cause of blood loss is believed to result mostly from occult GI blood

Table 1. Baseline characteristics of 103 patients

Characteristic	Result
Age, mean $\pm$ SD (years)	63.6 $\pm$ 15.2
Sex, n (male:female)	33:70
Hemoglobin, mean $\pm$ SD (g/dl)	7.61 $\pm$ 2.12
GI symptoms, n (%)	39 (38)
Upper alone	21 (20)
Lower alone	8 (8)
Upper and lower	10 (10)
Endoscopy, n (%)	
EGD alone	4 (4)
Colonoscopy alone	13 (13)
Bidirectional endoscopy	86 (84)

Table 2. Prevalence of significant GI lesions in 103 patients

Lesions	Number of patients (%)
Significant lesions	58 (56)
Single lesion	46 (45)
by EGD	32 (31)
by colonoscopy	14 (14)
Dual lesions	12 (12)
Insignificant lesions	26 (25)
Normal	19 (18)

Table 3. Endoscopic findings of 103 patients

EGD (n = 90)			
Significant lesions	n (%)	Insignificant lesions	n (%)
GU, DU (≥ 1 cm or ≥ 2 ulcers ≥ 0.5 cm)	20 (22)	Small esophageal varices	5 (6)
Erosive gastritis	18 (20)	Small ulcer	4 (4)
GERD LA grade C-D	1 (1)	Hyperplastic polyp	2 (2)
Gastric carcinoma	4 (4)	GERD LA grade A-B	8 (9)
		Submucosal mass	1 (1)
		Nonerosive gastritis	8 (9)
Colonoscopy (n = 99)			
Significant lesions	n (%)	Insignificant lesions	n (%)
Colonic carcinoma	13 (13)	Polyp < 1.5 cm	6 (6)
Polyp ≥ 1.5 cm	4 (4)	Diverticulum	6 (6)
Ulcer	8 (8)	Lipoma	1 (1)
Angiodysplasia	1 (1)	Parasites	2 (2)
		Hemorrhoids	7 (7)

Table 4. Univariate analysis of factors associated with significant GI lesions

Factors	Significant lesions (n = 58)	Insignificant lesions or normal (n = 45)	Odds ratio (95% CI)	p-value
Age, mean ± SD (year)	65.2 ± 14.1	61.6 ± 16.4	-	0.231
Male gender, n (%)	19 (33)	14 (31)	0.93 (0.40-2.14)	0.859
Hemoglobin level,				
Mean ± SD (g/dl)	7.51 ± 2.11	7.75 ± 2.14	-	0.562
< 10 g/dl, n (%)	53 (91)	38 (84)	1.95 (0.58-6.62)	0.277
GI symptoms, n (%)	26 (45)	13 (29)	2.20 (0.81-4.98)	0.098
Anti-platelet use, n (%)	30 (52)	14 (31)	2.37 (1.05-5.36)	0.036
Positive FOBT, n (%)*	34/42 (81)	24/40 (60)	2.83 (1.05-7.68)	0.038

* FOBT was done in 82 patients

loss. Bidirectional endoscopy (*i.e.,* EGD and colonoscopy) is therefore the mainstay investigations. However, the appropriateness of this strategy for IDA patients in Thailand is unknown because the sites and types of GI lesions may differ and the prevalence of colorectal carcinoma is found to be lower than Western population. In an attempt to establish an appropriate guideline, the authors prospectively studied 103 patients with IDA using bidirectional endoscopy.

The present study identified significant GI lesions in 56% of patients. This prevalence is close to the results of Western studies (40-84%)[3-8] and that of Ovartlanporn's study[9] (49%), but quite different from Sophonthanasiri's study[10] (17%). The differing criteria of IDA and geographic variation may contribute to the disparity of the prevalence of GI lesions. The use of looser criteria for IDA (*e.g.* low transferrin iron saturation alone) used by Sophonthanisiri's study (causing the chance of including some patients with anemia of chronic disease) and the different geography[10] may result in the lower prevalence of GI lesions.

The results of the present study confirms the findings of most other studies which showed that EGD has a higher yield of GI lesions than colonoscopy,

(43% versus 25%), and dual lesions were found in 12%. The most common identifiable causes from EGD and colonoscopy were peptic ulcers and colonic carcinoma, respectively. These results were similar to that of Western studies[3-8].

The value of using site-specific symptoms to guide the route of endoscopy is controversial. The present study observed that these symptoms might help guiding the initial route of endoscopy because they could predict the lesions correctly in 60 to 80% of cases. In patients without GI symptoms, significant upper GI lesions were more commonly found than lower GI lesions (39% vs. 17%). Thus, EGD may be more appropriate to be the initial endoscopy in patients without guiding symptoms in Thailand.

Another unclear issue is the definition of significant GI lesions that are considered definite causes of IDA and preclude the need of further endoscopy via another route. In the present study, the authors used a well-accepted definition by Rockey et al[6]. Nevertheless, in patients older than 50 years old, the authors chose to perform bidirectional endoscopy in every patient unless cancer was detected by the initial endoscopy as this approach was recommended by the British Society of Gastroenterology guideline[1]. Results of the present study also supported this approach, for example, among the 20 patients with PU detected by EGD, four patients (20%) had colonic carcinoma or large colonic polyps, and they would have been missed if colonoscopy were not performed.

The present study identified two predictors for the presence of significant GI lesions, anti-platelets use, and the positive FOBT. However, the associations were not strong and the values in predicting GI lesions of these factors, particularly the FOBT were not good enough to change the clinician's decision on whether to perform endoscopy. The endoscopy is eventually required in every patient with IDA regardless of the result of FOBT.

There are some limitations in the present study. Firstly, the study was conducted in the university hospital setting, thus the results may not be able to generalize to others where the prevalence of the diseases may differ. A large multicenter study may be needed to clarify the real prevalence. Secondly, the present study did not further investigate the small bowel in patients with negative bidirectional endoscopy *e.g.* by capsule endoscopy (CE), double-balloon enteroscopy (DBE) or single balloon enteroscopy (SBE). It has been shown that CE and DBE may discover the small bowel causes of IDA in ~50-60% of patients investigated[11-13]. Thus, the true prevalence of GI lesions in IDA patients should be higher.

In conclusion, the prevalence of GI tract lesions in Thai IDA patients evaluated by bidirectional endoscopy is 56%. Peptic ulcers and colorectal cancer are the two most common causes. EGD has higher yield than colonoscopy and is the preferred initial endoscopy unless there are suggestive site-specific symptoms. Dual lesions are common, thus bidirectional endoscopy is required in most patients (particularly elderly) unless cancer is detected from the initial endoscopy. No factors can reliably predict the presence of GI lesions or help in selecting the route of endoscopy.

Potential conflicts of interest

None.

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การตรวจหารอยโรคในทางเดินอาหารโดยการส่องกล้องสองทางในผู้ป่วยที่มีภาวะเลือดจางจากการขาดธาตุเหล็ก

สุพจน์ พงศ์ประสบชัย, ทัศนีย์ ศรีประยูร, สถาพร มานัสสถิตย์

ภูมิหลัง: *ภาวะเลือดออกแฝงจากทางเดินอาหารเป็นสาเหตุที่พบบ่อยของภาวะเลือดจางจากการขาดธาตุเหล็ก ข้อมูลเกี่ยวกับอุบัติการณ์และยุทธศาสตร์ที่เหมาะสมในการประเมินภาวะเลือดจางจากขาดธาตุเหล็กในประเทศยังมีน้อย การศึกษานี้มีวัตถุประสงค์เพื่อประเมินภาวะเลือดจางจากขาดธาตุเหล็กสำหรับรอยโรคในทางเดินอาหารโดยการส่องกล้องสองทาง*

วัสดุและวิธีการ: *ผู้ป่วยที่มีภาวะเลือดจางจากขาดธาตุเหล็ก ได้รับการตรวจส่องกล้องทางเดินอาหารส่วนบนและส่องกล้องลำไส้ใหญ่เพื่อหารอยโรคที่มีนัยสำคัญ ข้อมูลทางคลินิกและผลตรวจเลือดแฝงในอุจจาระจะได้รับการบันทึกเพื่อหาปัจจัยที่สัมพันธ์กับการพบรอยโรคในทางเดินอาหาร*

ผลการศึกษา: *ผู้ป่วย 103 ราย มีอายุเฉลี่ย 63.6 ± 15.2 ปี พบรอยโรคที่มีนัยสำคัญ 58 ราย (ร้อยละ 56) โดยร้อยละ 43 พบจากการส่องกล้องทางเดินอาหารส่วนบน และร้อยละ 25 พบจากการส่องกล้องลำไส้ใหญ่ ผู้ป่วย 12 ราย (ร้อยละ 12) พบรอยโรคจากทั้งสองทาง สาเหตุที่พบบ่อยที่สุดคือแผลเป็ปติก (ร้อยละ 22) และมะเร็งลำไส้ใหญ่ (ร้อยละ 13) ประวัติการใช้ยาต้านเกล็ดเลือดและการตรวจพบเลือดแฝงในอุจจาระมีความสัมพันธ์กับการพบรอยโรคในทางเดินอาหารด้วย odds ratio 2.37 (ค่าความเชื่อมั่นร้อยละ 95 1.05-5.36, ค่าพี 0.036) และ 2.83 (ค่าความเชื่อมั่นร้อยละ 95 1.05-7.68, ค่าพี 0.038) ตามลำดับ การตรวจเลือดแฝงในอุจจาระมีความไว ความจำเพาะ positive predictive value และ negative predictive value สำหรับการมีรอยโรคทางเดินอาหารร้อยละ 81, 40, 68 และ 66 ตามลำดับ อาการที่จำเพาะต่อตำแหน่งทางเดินอาหารช่วยชี้แนะการเลือกทางส่องกล้องได้อย่างถูกต้องในร้อยละ 60-80 ของผู้ป่วย*

สรุป: *การส่องกล้องทางเดินอาหารส่วนบนตรวจพบรอยโรคได้มากกว่าการส่องกล้องลำไส้ใหญ่ และน่าจะเป็นการส่องกล้องอันดับแรกเว้นแต่มีอาการที่จำเพาะต่อตำแหน่งทางเดินอาหาร การส่องกล้องสองทางมักต้องทำในผู้ป่วยส่วนใหญ่ยกเว้นกรณีที่การส่องกล้องทางแรกพบมะเร็ง*