



Evaluation for Gastrointestinal Tract Lesion in Patients with Iron Deficiency Anemia

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ABSTRACT

Background: Occult bleeding from the gastrointestinal tract is believed to be the most common cause of iron-deficiency anemia (IDA) in patients without an obvious source of blood loss. In general, when a clinician sees a patient with IDA, a fecal occult blood test (FOBT) is sent. If it is positive, the patient will be recommended to undergo esophago-gastro-duodenoscopy (EGD), colonoscopy will be done also if EGD is negative. There are a few studies exploring the usefulness of this practice. This study was conducted to assess the prevalence and the sites of the gastrointestinal lesions that may cause occult bleeding in IDA Thai patients, and also to assess the efficacy of two types of FOBT(immuno-based and guaiac-based) in detecting GI bleeding in this population.

Methods: During a 10 months period we prospectively studied 69 patients with iron-deficiency anemia. We tested FOBT using guaiac-based randomly, then repeat it after 72-hour diet restriction, by using immunobased test. All underwent EGD Colonoscopy was performed in patients with a negative EGD. For patients with negative endoscopic studies, small bowel study or capsule endoscopy were further studied.

Results: Fifty-one patients had a positive random guaiac-based FOBT. After diet restrictions, the positive results decreased to 28 positive tests. Immuno-based FOBT were positive in 20 patients. The agreement percentage between random and diet-restricted FOBT was 60.9%. Gastrointestinal endoscopy revealed at least one lesion that potentially responsible for blood loss in 12 of the 69 patients (17.4%). EGD revealed bleeding sources in 9 patients, and colonoscopy revealed in 4 patients. One patient had lesions in both upper and lower gastrointestinal tracts.

Conclusions: Among Thai IDA patients without obvious or active bleeding who were referred for further evaluation, the prevalence of gastrointestinal lesions is much lower than in the West. Upper gastrointestinal lesions are more readily identified. Although more specific, the immuno-based FOBT is less sensitive than the guaiac-based test.

Key words : iron deficiency anemia, endoscopy, gastrointestinal tract, fecal occult blood test

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INTRODUCTION

Occult bleeding from the gastrointestinal tract is widely believed to be the most common cause of irondeficiency anemia (IDA) in patients without an obvious source of blood loss⁽¹⁻⁴⁾. Usually this "gastrointestinal tract blood loss" is suspected by a positive guaiacbased fecal occult blood tests (FOBT)⁽⁵⁻⁷⁾. In general clinical practice, when a clinician sees patient with IDA, an FOBT is taken. If the FOBT is positive, the patient will be sent for an esophago-gastro-duodenoscopy (EGD). And if EGD is negative, colonoscopy will be further requested. However, several reports found that the endoscopic results did not correspond well with the FOBT results⁽⁶⁾. This may be explained by a false positive FOBT (usually from certain food), bleeding from the site that cannot be accessed by EGD and colonoscopy (e.g., small intestine), the lesion which disappeared before endoscopic examination, and the poor skill of the endoscopist.

As this scheme has been routinely practiced for a long time, there have been not so many studies exploring its usefulness and cost-effectiveness. We reviewed the relevant literature, and found that previous studies in patients with IDA from the Western countries were performed in rather non-homogeneous populations, along with an assortment of endoscopic techniques. Hence the outcome can be so varied with diverse results and recommendations, such as various frequency and sites of the lesions^(1,3,4,8), the cost-effectiveness of bidirectional endoscopy⁽⁹⁻¹¹⁾, high rate of false negative of FOBT, 3 dietary effect to guaiac-based FOBT result⁽¹²⁻¹⁴⁾, and variations in the efficacy of the immuno-based FOBT⁽¹⁵⁻¹⁹⁾.

As there are certain (albeit varied) data from Western countries, it appears that such data in Thailand are scarce. The routine practice of the clinician as mentioned above may not be suitable especially if the prevalence of gastrointestinal lesion is low. This study was conducted, to assess the prevalence and the sites of the gastrointestinal lesions that may cause occult bleeding in IDA Thai patients. We also compared the efficacy of two types of FOBT (immuno-based and guaiac-based) in detecting GI bleeding in such population.

PATIENTS AND METHOD

Patients

This is a prospective study. All adult patients with

iron-deficiency anemia who were referred to the Gastroenterology Division of Maharaj Nakorn Chiang Mai Hospital for further investigation between February 2005 and November 2005 were invited to participate in the study.

Iron deficiency anemia was defined as a hemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women, accompanied with a transferrin saturation of less than 15%.

Exclusion criteria were: an obvious cause of blood loss (e.g. epistaxis, heavy menstrual flow), active gastrointestinal hemorrhage, active infection or inflammatory disease, severe cardiopulmonary disease, age under 18 years, and inability or un willingness to give informed consent for the study.

Detailed clinical data were obtained from all enrolled patients, with emphasis on gastrointestinal symptoms. The symptoms of the upper gastrointestinal tract that patients were asked about were dyspepsia, odynophagia, heart burn, dyspepsia, nausea, vomiting, anorexia and upper abdominal pain related to eating or relieved by antacids. The lower gastrointestinal symptoms inquired were hematochezia, changes in bowel habit, diarrhea, constipation and colicky abdominal pain and altered the passage of stool. Patients were also asked about the use of aspirin, NSAIDs, tobacco and alcohol.

The study was approved by the Research Ethics Committee of The faculty of Medicine, Chiang Mai University.

Fecal occult blood test

After informed consent was taken, the first stool samples were tested for occult blood with guaiac-based fecal occult blood test. Patients were then informed to strictly avoid any food or drug that may cause even minute bleeding or interfere with fecal occult blood test such as NSAIDs (including aspirin), antacids, steroids, iron supplements, vitamin C, citrus fruits and other foods containing large amounts of vitamin C for the next 72 hours. Foods like red meats, animal blood products, uncooked broccoli, uncooked turnips, cauliflower, uncooked cantaloupe, uncooked radish and horseradish and parsnips must also be avoided and not taken during this 72 hours period.⁽¹⁴⁾

The stool samples were collected during 72 hours (2 samples each day) for guaiac-based and one more sample on the third day for immuno-based fecal occulted blood test.



Endoscopy

After all fecal occult blood tests were taken, esophago-gastro-duodenoscopy (EGD) was performed in all patients, and if a lesion(s) was/were detected and reasonably and satisfactorily explained the cause of bleeding, the patients was treated accordingly, without any further investigation. But if otherwise, total colonoscopy was performed on the same day. Cases that both the upper and the lower endoscopic examinations were negative were referred to the Department of Radiology for small bowel follow through study⁽²⁰⁾ or capsule endoscopy⁽²¹⁾ (if affordable).

For the endoscopic examination of the upper intestinal tract, the lesions considered to be sources of blood loss were carcinoma, esophagitis with erosions or ulceration involving ≥ 10 percent of the distal 5 cm of the esophageal mucosal surface (grade 3 or 4 esophagitis) erosive gastritis or duodenitis (defined as at least 50 erosions ≥ 1 mm in diameter with white bases encircled by erythema), single duodenal or gastric ulcer ≥ 1 cm in diameter or two ulcers ≥ 0.5 cm in diameter (measured with expanded biopsy forceps), adenomas, and vascular ectasias.⁽⁸⁾

For colonoscopic examinations, the following lesions were judged to be sources of substantial occult blood loss: a carcinoma, one or more adenomatous polyps over 1.5 cm. in diameter, vascular ectasias that numbered five or more or were at least 8 mm. in diameter, active colitis, or a colonic ulcer more than 1 cm. in diameter. Diverticula with out bleeding stigmata were judged not to be a source of blood loss⁽⁸⁾.

In patients who underwent a small bowel follow through or a capsule endoscopy, mass lesion or lesion more than 1 cm. in diameter, ulcerations, hemorrhagic mucosa and extensive mucosal inflammatory changes were judged to be propable sources of blood loss⁽¹²⁾.

Statistical analysis

Sample size

As the study was the first done in Thailand, we calculated the sample size as follow:

n = $[Z^2 \alpha/2 p (1-p)] / e^2$ = $[(1.96)^2 (0.6) (0.4)] / 0.12$ = 92

Where, n =sample size

p = suspected rate of the lesion potentially responsible for blood loss, estimated to be 60%, as previously reported in the literature⁽¹²⁾

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- $Z = \text{confidence coefficient, } 1.96 \text{ (from } \alpha \text{-} \text{error} = 0.05\text{)}$
- e = precision of estimation, 0.1 (as per the limitation of time period and the number of about 6-8 patients a month)

Statistical methods

Data were presented as number, frequency, and percentage. Descriptive statistic was used where appropriate. Sensitivity, specificity, false positive, positive and negative predictive value were calculated for both fecal occult blood tests, taking the endoscopic result as gold standard. We also looked for an agreement percentage between the random FOBT and the diet-restricted FOBT.

RESULTS

During the study period, 97 patients were referred to the Gastroenterology Division for evaluation of iron deficiency anemia. Twenty eight patients were excluded, 14 did not meet the criteria for iron deficiency anemia, and 8 had chronic active infection and/or inflammatory disease. The remaining 6 were excluded because they lost to follow up during the investigation period. The study flow is summarized in Figure 1.

Clinical features

Among 69 patients, 23 (33.3%) were male and 46 (66.7%) were female. The median age was 65 years, with a range of 21-83 years. None of the women were menstruating. All patients had hemoglobin levels and transferrin saturation that were consistent with iron deficiency anemia.

Twenty-one patients had concomitant medical illnesses : 4 diabetes, 9 coronary heart disease, 3 hypertension, 2 chronic renal failure, 2 chronic obstructive pulmonary disease, and 1 progressive systemic sclerosis.

Four patients had history of recent alcohol drinking. Two patients smoked. Eight patients recently used NSAID, eleven took aspirin regularly, and one took anticoagulant.

For symptoms, four had a history of dyspepsia, three had diarrhea, one was constipated, another had history of lower abdominal pain, and nine had significant weight loss. No one had heartburn, dysphagia or vomiting.

Significant gastrointestinal lesions were detected

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Figure 1 Flow chart and result of the study

in 12 of the 69 patients (17.4%). Esophago-gastroduodenoscopy demonstrated significant lesion(s) in 9 patients (13%) whereas colonoscopy demonstrated significant lesion(s) in 4 (5.8%). The details of the endoscopic results were as follow : 9 had upper GI tract lesions, (3 of them had a history of dyspepsia), 4 had lower GI tract lesions (2 of them had a history of diarrhea).

Fecal occult blood test

The random first time guaiac-based fecal occult blood test was positive in 51 patients. But only 11 of these 51 patients had a significant lesion (s). Among the negative 18 patients, only 1 had a significant endoscopic lesion. The calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the first random fecal occult blood test in this study were 91.7%, 29.8%, 21.6% and 94.4% respectively.

After 72-hour diet restriction, the repeat fecal occult blood was positive in 28 patients, much reduced from 51. Nine of the 28 positive cases had significant endoscopic findings. Meanwhile, the negative test increased from previously 18 to 41. The calculated sensitivity, specificity, PPV and NPV of the diet-restricted guaiac-based FOBT were 75.0%, 66.7%, 32.0% and 92.0% respectively.

The immuno-based fecal occult blood test was positive (20 patient), 6 of whom had a significant lesion(s), while 6 of the 49 negative immuno-based FOBT patients had positive lesion(s). The calculated sensitivity, specificity, PPV and NPV of the immuno-based FOBT were 50.0%, 75.4%, 30.0% and 87.8%, respectively.

Taking into account that the immuno-based FOBT is more sensitive in lower GI tract bleeding, we com-

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Random guaiac-based	91.7	29.8	21.6	94.4
Diet-restricted guaiac-based	75.0	66.7	32.0	92.0
Immuno-based, overall	50.0	75.4	38.0	87.8
Immuno-based, upper GI	75.0	73.0	15.0	97.0
Immuno-based, lower GI	74.4	73.3	20.0	89.8

Table 1 Comparison of various techniques of FOBT

pared the sensitivity, specificity, PPV and NPV of the immuno-based FOBT in the lower GI lesions to those corresponding values in the upper GI lesions. These were 75.0%, 73.0%, 15.0% and 97.0%, as compared to 44.4%, 73.3%, 20.0% and 89.8%, respectively. The comparison of various FOBT techniques is shown in Table 1.

The agreement percentage between the random and the diet-restricted guaiac-based FOBT was 60.9%.

Endoscopic findings

In 9 patients with upper gastrointestinal tract lesions, one had a large gastric ulcer at the antrum without active bleeding. This patient also had a severe active non-specific colitis at the distal part of colon (colonoscopy was performed because of a history of diarrhea). One patient had a gastric ulcer with oozing blood and the bleeding was stopped by endoscopic treatment. One patient had two small duodenal ulcers. One patients had severe hemorrhage gastritis of the entire gastric mucosa. One patients had a severe LA class C esophagitis. We found 3 patients with cancer. (1 signet ring cell carcinoma of the stomach presenting as ulcerated mass at the gastric cardia, 1 moderately differentiated adenocarcinoma of the stomach presenting as infiltrative mass lesion at gastric antrum, 1 poorly differentiated adenocarcinoma presenting as an ulcerated mass at the duodenal bulb).

In the four patients with colonoscopic lesions, one had carcinoma of the descending colon, another had carcinoma at rectum (both presenting as ulcerated mass lesion), two had severe nonspecific colitis at the ascending colon and the distal colon.

Only one case underwent capsule endoscopy. Surprisingly this patient had a diffuse large B cell lymphoma presenting as nodular mucosa of distal jejunum and ileum causing the narrowing of the intestinal lumen. This patient had exploratory laparotomy and small bowel resection. All 12 patients with positive findings were treated as per standard care. The patient with B cell lymphoma detected by capsule endoscopy died after 2 month of treatment.

The remaining 57 patients with no definite cause for chronic blood loss were empirically treated with oral iron supplement, and were seen 1-6 months later. Iron deficiency anemia resolved in 54. Three others who were not improved had underlying diseases (2 chronic renal failure, 1 progressive systemic sclerosis) and were reevaluated by the hematologist.

DISCUSSION

This is the first study in Thailand on the prevalence of gastrointestinal lesions that can cause iron deficiency anemia. It is done in the university hospital, where all evaluations were done quite carefully. From this study the prevalence of GI lesion was rather low, 17.4% overall. The prevalence of upper gastrointestinal lesions was 13%, substantially greater than that of lower gastrointestinal lesions, 5.8%. These data were much different from previously studied data in Western countries, such as that by Don C. Rockey in 1993 reported upper gastrointestinal tract as a bleeding source in 36% of patients while colonoscopy detectied a lesion in 25%.⁽¹²⁾ The colonic cancer prevalence from this latter study was much higher than this study. This may partly explain the above difference.

The low prevalence from this study may be either a true low prevalence or may be due to resolution of those benign lesions that spontaneously resolved within 72 hours of diet restriction for the second fecal occult blood test, and/or small intestinal lesions undetected by radiologic studies such as vascular ectasia or small mucosal lesion in the small intestine.

The random guaiac-based fecal occult blood test without diet restriction in this study yielded a very high sensitivity, but very low specificity. This intern results to the low positive predictive value and the high negative predictive value. We expected that diet restriction might improve the guaiac-based FOBT, but we found that although the specificity was slightly improved, the sensitivity dropped to some degree, with the agreement percentage between the two tests was only 61%.

From above, we recommended that the guaiacbased test may not be required for screening gastrointestinal blood loss in iron deficiency anemia, as endoscopy is eventually performed in most of the patients anyway.

There were many studies about the efficacy of immuno-based fecal occult blood test compared to the conventional guaiac-based fecal occult blood test, including a recent meta-analysis.⁽¹⁵⁻¹⁹⁾ The results from these studies varied. Again, in our study, the immuno-based fecal occult blood test is not quite impressive as a screening tool. This may be explained by the high sensitivity only with respect to bleeding from the lower GI tract.

There are many limitations in our study, notably; the relatively small number of patients, and being a single-center study. It is hoped that larger studies involving several teams of health care givers may be conducted in the future. More funds are needed for expensive test such as capsule endoscopy. Novel screening test should be sought to replace the presently used FOBT.

In conclusion, this first from Thailand, the prevalence of GI sources of bleeding in iron deficiency anemia is much lower than in the West. FOBT that is commonly used was not optimal for screening, even with diet restriction, and immuno-based FOBT did not improve much of the efficacy. Further multicenter study is needed to clarify these findings.

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