

Enteroscopic Study for Evaluation of Small Intestinal Lesions in Patients with Unexplained Iron Deficiency Anemia

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ABSTRACT

Background: Iron deficiency anemia (IDA) is the most common cause of anemia worldwide. It is widely accepted that chronic occult blood loss from the gastrointestinal tract is a major cause of IDA. This study aimed to evaluate small intestinal lesions in patients with unexplained iron deficiency anemia, with or without fecal occult blood by enteroscopy and to elucidate the pathologic nature of small intestinal mucosal abnormalities for iron deficiency anemia. **Methods:** This study included 40 subjects; 10 non-anemic patients but suffering from GIT symptoms needed to be investigated by enteroscopy as a control group and 30 patients with unexplained iron deficiency anemia (without any bleeding sources detected by upper and lower gastrointestinal endoscopy). Complete blood count, iron status, and fecal occult blood test were measured. The small intestine was evaluated by push enteroscopy and histopathological examination for duodenum and jejunum mucosal biopsies was done. **Results:** Enteroscopic findings in IDA patients revealed that arteriovenous malformations were detected in 43.3%, jejunal varices in 6.7%, 3rd duodenal mass (tumor) in 3.3% and non-specific jejunal inflammation in 3.3%. There were moderate to severe lamina propria inflammation in all IDA patients that was significantly different from the control group. Logistic regression analysis showed that IDA was related to body mass index, enteroscopic and histopathologic lesions. **Conclusions:** Subjects with iron deficiency anemia after negative workup on the bleeding sources by conventional upper and lower endoscopies should undergo a further investigation of the small intestine by enteroscopic study, irrespective of their fecal occult blood status.

Keywords: Unexplained iron deficiency anemia , Enteroscopy , Small bowel

INTRODUCTION

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide, causing significant disease-related morbidity, and has a negative impact on patient's well-being and overall outcome. The prevalence of IDA in developed countries is estimated to be 2-5% of adult men and post-

menopausal women. ⁽¹⁾ It is widely accepted that chronic blood loss from the gastrointestinal tract is a major cause of IDA. ⁽²⁾

The evaluating methods for IDA patients are endoscopic and/or radiographic. Radiographic studies are generally effective for detecting masses and large ulcerating lesions, but

their sensitivity for vascular ectasies and more subtle mucosal lesions such as gastritis, esophagitis, and colitis is less than with endoscopic procedures. It is generally accepted that the current visualisation and imaging methods available to the gastroenterologist in diagnosing small bowel diseases and disorders are unsatisfactory.⁽³⁾ Since patients with IDA have a high pretest probability of disease, much of which is mucosal or will require biopsy, endoscopic investigation is the best first choice.⁽⁴⁾

One cross-sectional study investigating the gastrointestinal tract by gastroscopy and colonoscopy revealed that the incidence of bleeding sources in the gastrointestinal tract in patients with IDA was approximately 70%.⁽⁵⁾ Patients with occult gastrointestinal blood loss and IDA with negative work-up on gastroscopy and colonoscopy need comprehensive evaluation, including enteroscopy and capsule endoscopy.^(6,7) However, the prevalence of small intestinal abnormalities in patients with IDA without fecal occult blood is unclear.⁽⁸⁾

Capsule endoscopy (CE) has revolutionized the diagnostic workup for the small intestine. It is the least invasive procedure to investigate the entire small bowel and discovered many lesions including angioectasia, ulcer and tumor in the small intestine in patients with obscure gastrointestinal bleeding,^(9,10) while its disadvantages are the inability to perform biopsies or administer therapy, the potential for retention above a stricture, and the potential for missed lesions.

Enteroscopy is a method that allows direct visual inspection of the small bowel mucosa beyond the reach of standard upper endoscopies.⁽¹¹⁾ It can examine 80-120 cm beyond the ligament of Treitz and identify a source in 24-75% of patients with obscure bleeding.⁽¹²⁾ Enteroscopy is needed in patients with continued IDA despite a negative CE, and for biopsy and therapy of lesions demonstrated by CE.^(13,14)

In an attempt to evaluate small intestinal lesions in patients with iron deficiency anemia with or without fecal occult blood by enteroscopy and to elucidate the pathologic nature of small intestinal mucosal abnormalities for IDA, this work was designed.

The Pentax VSB-3440 was used for all examinations. This instrument is a video push-type enteroscopy, with a total length of 252 cm and a working length of 220 cm. Subjects are advised not to eat or drink anything for at least eight hours before the examination. They were placed in left lateral decubitus position for the procedure and enteroscopy was performed under standard light intravenous sedation. The majority of procedures were performed by a consultant.

The enteroscopy was introduced through the mouth, passed into the distal duodenum following the intubation of the pylorus, then the enteroscope was advanced through the duodenojejunal flexure and thereafter advancement techniques were similar to colonoscopy. The insertion of enteroscope into the small intestine was made by advancing the scope under direct luminal view and after the traverse of each bend. Observation for few hours after the procedure for early detection of any complication was done

PATIENTS AND METHODS

The study was carried out on 40 subjects divided into two groups: Group I: 10 non-anemic patients but suffering from GIT symptoms needed to be investigated by enteroscopy as a control group. Group II: 30 patients with unexplained iron deficiency anemia (without any bleeding sources detected by upper and lower gastrointestinal endoscopy). Iron deficiency anemia was diagnosed by hemoglobin level less than 13g/dL for males and 12 g/dL for females with a mean corpuscular

volume less than 80 fl with at least one of the following: a) Serum ferritin $\leq 25\mu\text{g/L}$. b) Transferrin saturation $< 20\%$ with iron concentration $\leq 8\mu\text{mol/L}$.⁽¹⁵⁾

The patients were attendants of the Internal Medicine Department, Tanta University Hospital. An informed consent was obtained from all participants in the research.

Exclusion criteria: Patients with other hematological disorders, obvious causes of IDA such as overt gastrointestinal bleeding or bleeding in gynecological organs, hepatic diseases or renal failure were excluded from the study.

All cases included in the study were subjected to the following: full history taking, complete clinical examination including gynecological screening in female patients to detect bleeding sources in gynecological organs, abdominal ultrasonography, laboratory investigations including: complete blood count, liver function tests, blood urea and serum creatinine, iron status (serum iron, serum ferritin, transferrin saturation & total iron binding capacity), complete stool analysis including fecal occult blood test.

Upper and lower gastrointestinal endoscopy for evaluation of bleeding sources & push enteroscopy with mucosal biopsy for histopathological examination were performed.

STATISTICAL ANALYSIS

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using numbers and percent. Quantitative data were described using range (minimum and maximum), mean and standard deviation. Comparisons between groups were made using Student's t-test or ANOVA for continuous variables. Multiple regression analysis was used to detect the most independent factor for IDA patients. The significance of the obtained results was judged at the 5% level.

RESULTS

In the present study, enteroscopic findings in IDA patients revealed that arteriovenous malformations were detected in 43.3% (Fig.1), jejunal varices in 6.7%, 3rd duodenal mass (tumor) in 3.3% (Fig.2) and non-specific jejunal inflammation in 3.3%. However, IDA patients showed no lesion in 43.3% with a statistically significant difference as compared to control group ($P=0.013$)(Table 3). The diagnostic yield of push enteroscopy for IDA patients in this study was 56.7 %.

In this study, there was no significant difference in IDA patients with GIT symptoms and those with non-GIT symptoms regarding enteroscopic findings. Moreover, there were no significant differences between IDA patients with positive and those with negative fecal occult blood test regarding enteroscopic findings except IDA patients with arteriovenous malformations ($P=0.023$). In addition, there were no significant differences in hemoglobin or serum ferritin levels among IDA patients with different enteroscopic findings.

Regarding histopathological examination of mucosal biopsies in the current study, the findings showed that villous crypt ratio (V:C) was normal in 43.3% of IDA patients, decreased in 40% and markedly decreased by 16.7% and was significantly different from the control group ($P=0.035$). Intraepithelial lymphocytes (IELs) were negative in 66.7% of IDA patients, 1+ in 16.7% and 2+ in 16.7% with no significant difference as compared to control group. There was moderate to severe lamina propria inflammation showing eosinophils, macrophages, and PMLs in all IDA patients that were significantly different from the control group ($P=0.037$). As regards epithelial cells, the malignant change was found in

3.3% of IDA patients, gastric metaplasia in 23.3% and no lesion was detected in 73.3 % with no significant difference as compared to control group (Table 5).

In this study, there was no significant difference in IDA patients with GIT symptoms and those with non-GIT symptoms regarding histopathological findings. Also, there was no significant difference in the villous crypt ratio or intraepithelial lymphocytes among IDA patients with different enteroscopic findings. Regarding inflammation and epithelial cells, there were significant differences in IDA patients with 3rd duodenal mass (tumor) by enteroscopy ($P=0.034$ & $P=0.039$, respectively). On the other hand, there were no significant differences between IDA patients with positive and those with negative fecal occult blood test regarding histopathological examination.

Logistic regression analysis showed that IDA was related to body mass index ($p=0.040$), enteroscopic lesions ($p=0.036$) and histopathologic lesions ($p=0.035$) (Table 6).

DISCUSSION

Iron deficiency is the most common cause of anemia, with the World Health Organization estimating it affects about 30% of the population worldwide (WHO, 2015).⁽¹⁶⁾ It is often secondary to chronic occult bleeding from the gastrointestinal tract and is a common reason for referral of patients to gastroenterologists.⁽¹⁷⁾

In clinical practice, esophagogastroduodenoscopy (EGD) and colonoscopy are performed in the initial evaluation of IDA to exclude a source of chronic blood loss from the GI tract. Despite undergoing standard endoscopic evaluation, up to 30% of patients with IDA have no definitive diagnosis.^(17,18)

It is generally accepted that the current visualization and imaging methods available to the gastroenterologist in diagnosing small bowel diseases and disorders are unsatisfactory.⁽³⁾ Since patients with IDA have a high pretest probability of disease, much of which is mucosal or will require biopsy, the endoscopic investigation is the best first choice.⁽⁴⁾

Enteroscopy, a rapidly evolving field, has had a significant Renaissance recently and the small bowel is no longer the black box for the endoscopist or the final frontier.^(19,20) This method allows direct visual inspection of the small bowel mucosa beyond the reach of standard upper endoscopies. It can examine 80- 120 cm beyond the ligament of Treitz and identify a source in 24- 75% of patients with obscure bleeding.⁽¹²⁾ Enteroscopy is needed in patients with continued IDA despite negative capsule endoscopy (CE), and for biopsy and therapy of lesions demonstrated by CE.⁽²⁰⁾

This study was conducted to evaluate small intestinal lesions in patients with unexplained iron deficiency anemia, with or without fecal occult blood by enteroscopy after negative work-up on the bleeding source by conventional upper and lower endoscopies and to elucidate the pathologic nature of small intestinal mucosal abnormalities for iron deficiency anemia.

In the present study, enteroscopic findings in IDA patients revealed that arteriovenous malformations were detected in 43.3%, jejunal varices in 6.7%, 3rd duodenal mass (tumor) in 3.3% and non-specific jejunal inflammation in 3.3%. However, IDA patients showed no lesion in 43.3% with a statistically significant difference as compared to control group ($P=0.013$). There were no significant differences between IDA patients with positive and those with negative fecal occult blood test regarding enteroscopic findings except IDA patients with arteriovenous malformations ($P=0.023$). The present study

indicates that even IDA patients with negative fecal occult blood test should undergo enteroscopy.

These findings are in agreement with Yamada et al.(2011),⁽⁸⁾ who revealed that the prevalence of small intestinal lesions including angioectasia, ulcers, and tumors in Japanese patients with IDA was approximately 50% and that there was no significant association between small intestinal lesions and fecal occult blood. Also, one European prospective study reported that 57% of IDA patients had small intestinal lesions.⁽⁷⁾ Moreover, Muhammed et al. (2009),⁽²¹⁾ retrospectively investigated IDA patients in the United States and reported that the incidence of small intestinal lesions was 59-69%. The current data suggest that the incidence of small intestinal lesions in IDA is globally similar.

Furthermore, Chak et al. (1998),⁽¹¹⁾ found that performing push enteroscopy in combination with esophagogastroduodenoscopy (EGD) increased the diagnostic yield of the upper evaluation in asymptomatic patients with iron deficiency from 41% to 68%. They concluded that performance of push enteroscopy should be the preferred initial diagnostic test when evaluating the gastrointestinal tract of patients with iron deficiency anemia. Notably, Gostout (1993)⁽²²⁾ has recommended small bowel biopsies in all patients with iron deficiency to diagnose sprue.

Reportedly, a retrospective study showed no recurrence of anemia in 71% with endoscopic treatment performed by push enteroscopy after 18 months of follow-up. However, if push enteroscopy showed no lesion, further explorations were unnecessary because the anemia did not recur in the majority (63%) of cases.⁽²³⁾

Recently, Sidhu et al. (2015),⁽²⁴⁾ have demonstrated that the diagnostic yield of capsule endoscopy in patients under 50 years of age with recurrent IDA was 28%. Significant pathology identified in this group included small bowel tumors, ulcers, and angioectasia. They reported that angioectasia is the second commonest finding after erosions and ulcers and that small bowel tumor were found in 3% of patients which is similar to findings by Koulaouzidis et al. (2012).⁽²⁵⁾

Interestingly, Zakaria et al. (2009),⁽²⁶⁾ evaluated the role of capsule endoscopy (CE) in obscure gastrointestinal bleeding (OGIB) and found that the diagnostic yield of CE in cases of OGIB was 56.1% and that the commonest lesions were angiodysplasias (17.5%), examinations were negative for lesions in 35.1% while capsule retention occurred in 3.5%. They concluded that capsule examination should be done after competent exhaustion of other diagnostic tools including upper and lower endoscopic examinations after proper bowel preparation in order to increase the diagnostic yield. They recommended repeat upper endoscopy and full colonoscopy with terminal ileoscopy before proceeding to capsule examination due to the high cost of capsule examination in our country.

CONCLUSION

Subjects with iron deficiency anemia after negative work-up on the bleeding sources by conventional upper and lower endoscopies should undergo a further investigation of the small intestine by enteroscopic study, irrespective of their fecal occult blood status. The performance of push enteroscopy and small intestinal mucosal biopsies in combination with bidirectional endoscopy is a helpful tool in the diagnosis of unexplained iron deficiency anemia. Clearly, further well-designed prospective studies in order to better evaluate the long-term clinical outcomes, economic impact and patient

satisfaction levels of the small bowel diagnostic tests that are currently available would be warranted.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with this work.

Table (1): Clinical findings in the studied group

Findings	Control (n=10)	IDA patients (n=30)
Age (years)	44.5 ±13.22	46.13 ± 20.3
Sex (M/F)	4/6	10/20
BMI (Kg/m²)	23.8 ±3.43	21.3 ± 2.54
Duration of IDA (months)	-	18.5 ±17.11
Smoking n (%)	3 (30%)	5 (16.7%)
History of NSAIDs n (%)	2 (20%)	12 (40%)
Blood transfusion	-	8 (26.7%)
GIT symptoms n (%)		
Abdominal pain	5 (50%)	12 (40%)
Diarrhea	4 (40%)	4(13.3%)
Dyspepsia	2 (20%)	7 (23.3%)
Vomiting	6 (60%)	4 (13.3%)
Heart burn	4 (40%)	12 (40%)
Non GIT symptoms n (%)		
Pallor	-	26 (86.7%)
Dyspnea	-	7 (23.3%)
Palpitation	-	5 (16.7%)
Fatigue	-	15 (50%)
Weight loss	-	3 (10%)
Iron therapy n (%)		
Oral	-	4 (13.3%)
IV ferric dextran	-	12 (40%)
IV ferric sucrose	-	14 (46.7%)

Table (2): The mean values of serum iron, serum ferritin, transferrin saturation and total iron binding capacity in the studied groups

	Control (n= 10)	IDA patients (n= 30)	Test of significance	p
Serum iron ($\mu\text{g/dL}$)				
Range	71.0 – 139.0	20.0 – 75.0		
Mean \pm SD	94.20 \pm 19.15	38.40 \pm 13.95	t= 9.959	<0.001 *
Serum ferritin ($\mu\text{g/L}$)				
Range	84.0 – 209.0	1.40 – 271.0		
Mean \pm SD	136.80 \pm 48.96	22.0 \pm 48.54	Z= 4.377	<0.001 *
Transferrin Saturation (%)				
Range	19.0 – 40.0	2.0 – 20.0		
Mean \pm SD	29.80 \pm 6.66	7.12 \pm 4.40	Z= 4.659	<0.001 *
Total iron binding capacity ($\mu\text{g/dL}$)				
Range	260.0 – 453.0	324.0 – 583.0		
Mean \pm SD	328.40 \pm 54.32	473.80 \pm 57.35	t= 7.029	<0.001 *

t, p: t and p values for Student's t-test

Z, p: Z and p values for Mann-Whitney test

* Statistically significant $p \leq 0.05$

Table (3): Distribution of endoscopic findings among the studied groups

Endoscopic findings	Control (n= 10)		IDA patients (n= 30)		χ^2	P
	N	%	N	%		
Upper gastrointestinal endoscopy						
Not Done	5	50.0	0	0.0		
Sliding hiatal hernia	0	0.0	4	13.3		
No lesion	5	50.0	26	86.7		
Lower gastrointestinal endoscopy						
Not Done	6	60.0	0	0.0		
No lesion	4	40.0	30	100.0		
Enteroscopy						
Arteriovenous malformations	0	0.0	13	43.3	1.081	^{FE} p=0.560
Jejunal varices	0	0.0	2	6.7	0.702	^{FE} p=1.000
3 rd duodenal mass (tumor)	0	0.0	1	3.3	0.342	^{FE} p=1.000
Non-specific jejunal inflammation	1	10.0	1	3.3	0.702	^{FE} p=0.442
No lesion	9	90.0	13	43.3	6.599	^{FE} p=0.013*

□□: Chi square test □

FE: Fisher exact for Chi-square test

*Statistically significant p ≤ 0.05

Table (4): Small intestinal enteroscopic findings in IDA patients with and without fecal occult blood

Enteroscopic findings	Fecal occult blood test (FOBT)				Chi-square	
	Negative (n=19)		Positive (n=11)		χ^2	FE _P
	N	%	N	%		
Arteriovenous malformations	5	26.3	8	72.7	6.111	0.023*
Jejunal varices	2	10.5	0	0.0	1.241	0.520
3 rd duodenal mass (tumor)	0	0.0	1	9.1	1.787	0.367
Nonspecific jejunal inflammation	1	5.3	0	0.0	0.599	1.000
No lesion	11	57.9	2	18.2	4.474	0.057

FE: Fisher exact for Chi square test

* Statistically significant $p \leq 0.05$

Table (5): Histopathological findings among the studied groups

	Control (n= 10)		IDA patients (n= 30)		χ^2	MC p
	N	%	N	%		
Villous crypt ratio (V:C)						
Normal	9	90.0	13	43.3	5.547	0.035*
Decreased	1	10.0	12	40.0		
Marked decreased	0	0.0	5	16.7		
Intraepithelial lymphocytes (IELs)						
Negative	8	80.0	20	66.7	1.601	0.463
1+	2	20.0	5	16.7		
2+	0	0.0	5	16.7		
Inflammation						
1+	9	90.0	9	30.0	11.259	0.037*
2+ eosinophil	0	0.0	8	26.7		
2+ macrophage	0	0.0	1	3.3		
2+ macrophage &PMLs	1	10.0	8	26.7		
2+ macrophage and eosinophil	0	0.0	3	10.0		
Dense inflam. desmoplastic	0	0.0	1	3.3		
Epithelial cells						
Malignant	0	0.0	1	3.3	3.101	0.202
Gastric metaplasia	0	0.0	7	23.3		
No lesion	10	100.0	22	73.3		

χ^2 : Chi square test
 MC: Monte Carlo for Chi-square test
 *Statistically significant p \leq 0.05
 PMLs: Polymorphonuclear leukocytes
 1+: Moderate increase
 2+: Severe increase

Table (6): Odds ratios of IDA according to clinical characteristics, enteroscopic and histopathological findings

Variables	Odds ratio	95% CI		P-value
		LL	UL	
Age (Years)	0.280	0.240	1.040	0.513
BMI (Kg/m ²)	3.598	1.405	4.883	0.040*
Sex	0.589	0.060	2.748	0.649
Enteroscopic lesions	9.885	1.181	49.637	0.036*
Histopathologic lesions	7.881	1.162	41.826	0.035*

95%CI: 95%confidence interval calculated by logistic regression analysis

LL: Lower limit

UL: Upper limit

*Statistically significant $p \leq 0.05$



Fig.(1) Small intestinal arteriovenous malformations of the jejunum by push enteroscopy



Fig. (2): 3rd duodenal mass easily bleeds on touch by push enteroscopy

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