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A prospective study on the role of Bi-directional endoscopy in evaluating young males with Iron Deficiency Anemia

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Abstract

Aim: This study tried to assess the utility of Bi-directional endoscopy in the management algorithm of young adult males with Iron deficiency anemia (IDA). The main objective being, to study the diagnostic yield of upper and lower GI endoscopy in detecting the cause of iron deficiency

Material & Methods: The study was a hospital-based prospective observational study, which enrolled consecutive male patients (18-40 yrs) with IDA visiting a Tertiary care center. The study period was from Oct 2015 to Dec 2017. All patients underwent Upper GI endoscopy & Colonoscopy as part of the study protocol along with a standard work up for IDA. Data was collected and analyzed in SPSS version16, and standard descriptive statistics along with Analysis of variance (ANOVA) and Univariate followed by Multivariat analysis with logistic regression was done. The effort was to establish any statistically significant association between the study parameters and the outcome on endoscopies.

Results: 50 patients who met the inclusion criteria and gave their consent, were included in the study. Upper GI lesions were diagnosed in 13 men (26 %). Gastritis was the most common lesion (6), followed by Peptic ulcers (4) and Celiac disease (3). Significant lower GI tract lesions were diagnosed in 05 men (10 %). Inflammatory bowel disease was diagnosed in 2 men (2 %), followed by one each of adenomatous polyps , caecal tuberculosis and solitary rectal ulcer.

In univariate analysis, Lower hemoglobin levels, Fecal occult blood (FOB) positivity, and any GI symptoms were associated with the diagnosis of a significant GI lesion. In multivariate analysis with logistic regression, the presence of any GI symptoms ($p < 0.001$, OR 1.44, CI 0.112 – 0.394) and Fecal Occult Blood (FOB) Positivity ($p < 0.036$, CI 0.023 – 0.692) were found to be significantly associated with the diagnosis of clinically significant GI lesions on endoscopy.

Conclusion: This study on young males with IDA, shows that similar to other western studies, Indian subjects with IDA also have an increased prevalence of GI lesions, which are detectable on bidirectional endoscopy (18/50). The results of the study suggest that all young men with IDA should be evaluated with endoscopies & specific complaints may dictate the order of evaluation. Celiac serology (IgA TTG) was positive in 6% cases and should

be performed routinely in IDA cases even in our patients. In patients with IDA, those with low serum ferritin, positive GI symptoms, and positive fecal occult blood test, are more likely to have potentially correctable GI lesions on endoscopies.

Keywords: Anemia, Endoscopy, Ferritin

Introduction

Iron deficiency anemia (IDA) is a global public health problem which affects both the developing and the developed countries, and it is an indicator of poor nutrition and poor health with significant consequences for human health. Worldwide, at any given moment, more individuals have IDA than any other health problem. Globally, anemia affects 2 billion people, which corresponds to 24.8% of the worldwide population [1]. Anemia is one of the most common health problems in India which is much more prevalent in the rural than in the urban areas [2]. The prevalence in general population in India varies from 43 – 60% in adult males and 70-80% in young premenopausal females [3]. Poor nutrition, malabsorption of iron, malignancy and chronic blood loss are common causes of anemia in adults.

While menstruation is the most frequent cause in premenopausal women, chronic gastrointestinal blood loss is the commonest cause in post-menopausal women and males. Guidelines recommend evaluation by upper and lower GI endoscopy in adults with IDA. However, these recommendations are primarily based on studies involving elderly males and post-menopausal women with anemia and may not apply to young adults with anemia. Endoscopy, especially colonoscopy is an invasive procedure and should be done only if strongly indicated. There is a paucity of Indian literature on the causes of anemia in young adult males. This study intends to assess the utility of Bi-directional endoscopy (UGIE & Colonoscopy) in the management algorithm of young adult males with iron deficiency anemia.

Methodology

This was a hospital-based prospective observational study, which was carried out in males aged between 18–40 years from Oct 2015 to Dec 2017. Data was collected from consecutive patients with IDA meeting the inclusion criteria, attending medical services at this tertiary hospital in Southern India, during the study period.

Inclusion Criteria

1. Males, aged 18 - 40 years.
2. Iron Deficiency Anemia (IDA) defined by Hb< 13.0 g/dL and serum ferritin < 20 ng/ml.
3. No overt gastrointestinal bleeding.
4. Willing to give informed consent for Endoscopy & Colonscopy.

Exclusion Criteria

1. Co-morbidity that can explain anemia like CKD, Cirrhosis of liver, etc.
2. Any contraindication to endoscopic studies.

After taking a detailed history, a thorough clinical examination was done. Special emphasis on the history of any GI symptoms, dietary history, history of NSAID intake and anthropometry was done. Apart from routine Blood counts, Periphral blood smear, Liver function tests, Renal function tests & Blood sugars, special lab tests included Serum Ferritin, prothrombin Time with INR, IgA TTG antibodies and Stool Occult blood. Further each patient was subjected to USG Abdomen, UGI Endoscopy & Colonoscopy.

Gastric antral biopsy for H Pylori and duodenal biopsy was taken during UGI endoscopy, when no significant lesion was detected.Iron deficiency anemia was defined as hemoglobin level <13 g/dl and a serum ferritin level <20 ng/ml for the male study population. Celiac disease was diagnosed by characteristic pathological findings in

duodenal tissue samples and positive serology. HP infection was identified by the rapid urease test, or by identification of HP in tissue biopsies. Localization of abdominal symptoms to upper or lower GI tract was made after considering the patient's description and physical examination.Stool occult blood testing was done by using standard Benzidine test. Endoscopic procedures were performed in the left lateral position to prevent chances of aspiration. Heart rate, blood pressure and oxygen saturation were monitored during the procedure.

All UGIE were performed with topical pharyngeal anesthesia with oral lignocaine spray. All patients underwent colonoscopy with cecal intubation. Bleeding related endoscopic lesions were biopsied, and duodenal and gastric biopsies were taken if no lesions were found on endoscopy. All UGIE were performed with Fujinon EG-590U, serial number 74246A308 video scope and colonoscopies were performed with Fujinon EC-530WL, Serial number- 3C447B020 video scope. Following lesions were considered as source of IDA on UGI endoscopy: Esophagitis with erosions involving at least 5 mm of the mucosal surface of the esophagus, gastric and duodenal ulcers (>0.5 cm in diameter), carcinoma, adenomatous polyps (>0.5 cm in diameter), 5 or more vascular ectasias, erosive gastritis or duodenitis (defined as multiple mucosal defects encircled by erythema), and hiatus hernia with Cameron's erosions, portal hypertensive gastropathy and esophagogastric varices. Non-bleeding causes of Iron deficiency anemia included the following: histopathologically proven celiac disease. Helicobacter pylori-associated chronic gastritis and atrophic gastritis were considered as a possible causes of IDA only when all other causes were excluded.Analysis of variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients.

A Students t-test (two-tailed, independent) was used to find the significance of study parameters distributed on a continuous scale between two groups (Intergroup analysis). The Chi-square test was used to find the significance of study parameters distributed on a categorical scale between two or more groups. P value < 0.05 was taken as significant. The data collected was entered and analyzed in the Statistical software package SPSS 16.0.

Results

A total of 86 patients with microcytic hypochromic anemia were screened during this study period. Thirty six (36) patients were excluded due to various reasons (16 patients with an overt GI bleed, 12 patients with chronic illness that could explain the cause of anemia, 03 patients with normal serum ferritin level and 05 patients did not give consent for endoscopy). The remaining 50 patients who met the inclusion criteria and gave their approval were included for the study. These patients were subjected to upper and lower GI endoscopy.

a) **Baseline Clinical and Lab data (summarized in Table -1)**

Table – 1 (Baseline data)

Characteristic	Value
General	
Age(yrs)	30.76±6.42
Weight(kg)	69.64± 6.92
BMI(kg/m^2)	22.2 ± 4.1 (14.5–45.7)
Vegetarian	10 (20 %)
Hematological data	
Hemoglobin (g/dl)	9.52±2.51
TLC(per mm^3)	6774.20±2118.76
Platelet count(in lakhs/ mm^3)	3.11±1.28
Prothrombin time(sec)	12.13±1.34
INR	0.96±0.12
MCV (pl)	74.08±12.66
Ferritin (ng/ml)	10.41±5.57
Serum Creatinine (mg/dl)	0.96±0.19
Medications	
NSAID	04 (08 %)
Symptoms	
No symptoms	27 (54 %)
Upper GI symptoms	13 (26 %)
Lower GI symptoms	10 (20 %)

BMI- body mass index, NSAID - nonsteroidal anti-inflammatory drugs, TLC - total leucocyte count, MCV - mean corpuscular volume,Upper GI symptoms: heartburn and or epigastric pain, Lower GI symptoms: diarrhea, constipation, change in bowel habitss

b) **Upper GI Lesions**

Upper GI lesions were diagnosed in 13 men (26 %). The upper GI lesions diagnosed in the study population are summarized in Table 2. Gastritis was the most common finding, diagnosed in 06 subjects (12%). Endoscopic findings of subjects are shown in Table-2. Rapid Urease Test for H Pylori was done in all patients. A total of 16 patients were positive for H Pylori infection (Table-3). It was positive in all the 04 patients with gastroduodenal ulcers (100%) and 04 patients with gastritis (67%). The remaining 08 patients with positive RUT had normal endoscopy. Three (06%) patients had no obvious endoscopic lesion but on histopathological examination had features suggestive of celiac disease and were confirmed on serologic testing.

Table – 2 Upper GI Lesions

GI lesion	Number (%)
Gastritis	06 (12%)
Gastric ulcer	2 (4%)
Duodenal ulcer	2 (4%)
Celiac disease	03 (6%)

Table – 3 RUT & Upper GI Lesions

Endoscopic findings	Rapid Urease Test for H Pylori
Gastroduodenal Ulcers	04
Gastritis	04
Normal	08
Total	16

c) **Lower GI Lesions**

Significant lower GI tract lesions were diagnosed in 05 men (10 %). The lower GI lesions diagnosed in the study population are summarized in Table 4. Inflammatory bowel disease was diagnosed in 01 men (02 %), adenomatous polyps in 1 (02 %), deformed caecum (tuberculosis) in 01 (02 %) and solitary rectal ulcer in 01 (02%) patient. Benign or malignant tumors in the GI tract were not found in our study population.

Table – 4 Lower GI Lesions

Lower GI lesion	Number (%)
IBD	2 (4%)
Colonic Polyp	01 (2%)
Rectal ulcer	01(2%)
Deformed caecum(TB)	01(2%)

d) **GI Symptoms and Endoscopy findings**

Twenty three (46%) patients reported GI symptoms. Thirteen patients (26%) had upper GI symptoms, ten patients (20%) had lower GI symptoms. Upper GI symptoms were found in 77% (11/13) of patients with upper GI lesions. Only 8.1% (2/37) of asymptomatic subjects had positive endoscopic finding. Upper GI lesions were diagnosed more frequently when heartburn or epigastric pain were reported (Table 5).

Table – 5 UGIE Lesions and Symptoms.

Upper GI lesion	Heartburn and epigastric pain (13)	Asymptomatic or any other symptoms (37)
Erosive gastritis	4 (30.7 %)	2 (5.4 %)
Gastric ulcer	1 (7.6 %)	1 (2.7 %)
Duodenal ulcer	2 (15.3 %)	0
Celiac disease	3 (23%)	0
Any upper GI lesion	10(77%)	3(8.1%)

Likewise, lower GI lesions were diagnosed more commonly in men with the positive history of diarrhea, constipation or change in bowel habits. Lower GI symptoms were found in 40 % (04/10) patients with lower GI lesions. Only 2.5% (1/40) of asymptomatic subjects had positive colonoscopic finding. The prevalence of lower GI lesions among men according to specific GI symptoms is mentioned in Table-6.

Table -6 LGIE Lesions and Symptoms

Lower GI Lesion	Diarrhea, constipation, and change in bowel habits (10)	Asymptomatic or any other symptoms (40)
IBD	2 (20 %)	0
Colon poly	0	1 (2.5 %)
Deformed caecum	1(10%)	0
Solitary rectal ulcer	1 (10 %)	0
Any lower GI lesion	04(40%)	1(2.5%)

e) Univariate and Multivariate analysis

Table -7 summarizes the univariate analysis comparing the clinical and laboratory variables among men with or without significant GI lesions. Lower hemoglobin levels, Fecal occult blood (FOB) positivity, and any GI symptoms were associated with the diagnosis of a significant GI lesion. Moreover, significant GI lesions were diagnosed more frequently in men with Upper Gi symptoms of heartburn and epigastric pain (77 %, $p = 0.021$), and Lower GI symptoms of constipation or diarrhea (40 %, $p < 0.05$). Firther in univariate analysis, Low ferritin levels showed a trend towards the significance in predicting any GI lesions ($p = 0.06$).

Table-7 Univariate Analysis

Factors	No GI lesion (n = 32)	Significant GI lesion (n = 18)	*p*-value
Age (years)	29.83 ± 6.10	28.47 ± 7.32	0.49
BMI (kg/m^2)	23.12 ± 1.85	23.27 ± 2.22	0.9
Vegetarian	7	2	0.23
Hematological data			
Hemoglobin (g/dl)	10.46 ± 1.94	7.93 ± 2.65	**0.001 ***
MCV (pl)	70.6 ± 6.12	73.43 ± 4.72	0.33
Ferritin (ng/ml)	10.48 ± 4.64	7.25 ± 3.87	0.06
Symptoms			

Any GI symptom	6	17	**0.03***
FOB positive	1	6	**0.004 ***

Table- 8 summarizes the results of the multivariate analysis, using significant GI lesions was the outcome variable. The presence of GI symptoms ($p < 0.001$, OR 1.44, CI 0.112 – 0.394) and FOB Positivity (p <0.036, CI 0.023 – 0.692) were found to be significantly associated with the diagnosis of clinically significant GI lesions.

Table – 8 Multivaraite Logistic regression analysis

Predictor	*p*-value	95 % CI
Hemoglobin	0.717	0.23 - 0.33
Any GI symptom	**<0.001**	0.112 - 0.394
FOB Positive	**0.036**	0.023 - 0.692
Ferritin	0.075	0.23 - 0.33

Discussion

Over a third (36%) of young males with unexplained iron deficiency anemia had lesions on Bi=directional endoscopy. The majority (26%) had a lesion in upper GI tract while 10% had lesions in the lower GI tract. Gastritis, Gastroduodenal ulcers, Celiac disease, Inflammatory Bowel Disease, Solitary Rectal Ulcer, Colonic Polyp were the GI lesions noted in young males with iron-deficiency anemia. Young anemic males with heartburn and epigastric pain or altered bowels and FOB positivity, had a higher likelihood of a lesion on endoscopy. No hematological or biochemical parameter could predict the presence of a GI lesion in the study population. Helicobacter Pylori was detected in 16% of subjects who had normal endoscopy.

In this study, we report the results of prospective Endoscopic GI evaluation in 50 young male subjects with IDA. Significant GI lesions on endoscopy were diagnosed in 18 subjects (36%)of the study population. The reported prevalence of the diagnosis of significant GI lesions in bidirectional endoscopy for a mixed population under the age of 50 is 32.5 % (4),which is quite similar to the detection rate in this study. The detection rate of lesions in the upper GI tract lesions was more than lower GI tract (13 vs.05 respectively), in this study. This is similar to studies by Shahid Majid et al (5)**,** Kepczyk T et al (6)**,** Nahon S et al (7),where all of them found UGIE lesion in a higher percentage when compared to LGIE lesions. But a study by Dan Carter et al from Israel defense forces among 347 young men (18–40 years) with IDA, revealed the equal distribution of upper and lower GI lesions (8).

Lesions causing GI blood loss were the most common findings (30 %) in this study, simultaneously. lesions associated with iron malabsorption were also noted (Celiac disease 6%). Acid peptic disease was the most common GI pathology detected in the study population (20%). Likewise, in previous studies on upper GI lesions, mostly esophagitis, gastritis, duodenitis, gastric and duodenal ulcers, were reported to be a common finding in patients with IDA (9, 10). In our study, H Pylori infection was identified in 10 patients, and all of them had some lesion on endoscopy. H Pylori has previously been implicated as a cause of IDA [11,12], most probably due to the interference in the absorption of iron [13]. It was observed in this study that the chances of finding significant lesions on endoscopy were high in symptomatic subjects. Reporting of any Upper GI symptoms were found in 11/13 (84.6%) patients with upper GI lesions, and Lower GI symptoms were found in 04/05 (80%) patients with lower GI lesions. GI symptoms may help the clinician to determine the diagnostic approach as well as avoiding any unnecessary procedures. However, the association between specific symptoms and

the exact anatomical location of significant pathology is not yet clear. While a few studies have reported a strong correlation (14, 15), others did not (16, 17). In our study, the presence of GI-related symptoms was associated with an increase in the likelihood of identification of a GI lesion. The association of symptoms of heartburn and epigastric pain in the diagnosis of Upper GI lesions has previously been reported by a few authors (6,8); however, the association of diarrhea, constipation, and change in bowel habits to GI lesions has been reported in one study [17].

Another important finding in our study in Upper GI studies, was presence of Celiac disease (6 %) based on histology and IgA TTG positivity. The detection rate of celiac disease was higher than the reported prevalence in the general population (18,19). Similar higher detection rates have previously been reported in patients with IDA (20). As a tertiary care center, a possible referral bias must also be considered, as most our patients in this study were referred from peripheral health care facilities after basic investigations, for further evaluation of iron-deficiency anemia.

Inflammatory bowel disease (04%) was the major lower GI lesion detected in our study. Although, in previous studies, symptomatic hemorrhoids have been reported as one of the main causes of rectal bleeding and IDA (21,22) In the present study, we had excluded all patients with an overt GI bleed, and thus all these cases were probably left out as per protocol. IDA is a frequent complication of inflammatory bowel disease, with a reported prevalence of 16–68 % (23,24) It may be due to multiple mechanisms, including iron mal-absorption and chronic intestinal blood loss from inflamed mucosa. Another important finding of our study was the significant association between Fecal Occult blood (FOB) positivity and endoscopic findings. Significant GI lesion were detected in 85.7% of subjects with FOB positivity ($p<0.05$). This strong correlation stands to logic and is on expected lines.

Analyzing with univariate analysis, among the various indicators of iron deficiency anemia, which included bleeding and non bleeding related etiologies, lower hemoglobin levels (P=0.001), FOB positivity (P=0.03) and any GI symptoms ($p = 0.004$), were significantly associated with a GI lesion causing IDA. In the same analysis, low serum ferritin levels showed a trend towards significance ($p = 0.06$). Further, in Multivariate logistic regression analysis, after adjusting for confounding factors and controlling for all other variables, only GI symptoms ($p < 0.001$, OR 1.44, CI 0.112 – 0.394) and FOB Positivity ($p =0.036$, CI 0.023 – 0.692) were independent predictors of significant GI lesions on bi-directional endoscopy leading to IDA. There is scanty data regarding predictors of endoscopic lesions in IDA patients. However, low hemoglobin, low ferritin, female gender and history of NSAIDs have been shown to be associated with endoscopic lesions in patients with IDA having gastrointestinal symptoms [25,26]. In the present study, there was no statistically significant correlation of endoscopic findings with age, gender, Diet, BMI, Ferritin & MCV. The absence of any malignant lesions in this study , can be explained by the small sample (n=50) of young male population (18-40 yrs) enrolled for evaluation, where the prevalence of malignancy is very low.

The strengths of our study was a prospective design, with consecutive patients of IDA being enrolled, and comprehensive Bi-directional endoscopies being performed in all cases who were eligible. However, like any other study, we also had some limitations. Firstly, patients with positive endoscopic findings were not followed up with treatment, so that the temporal

association of the lesion and anemia could be confirmed. Secondly, further work-up of those patients who had no findings in endoscopy using enteroscopy or capsule endoscopy was not done. Thirdly, the small sample size with inherent referral bias in a Tertiary care setup need to be kept in mind while interpreting the results of this study.

Conclusion

This prospective observational study on young males with IDA, shows that similar to other western studies, Indian subjects with IDA also have an increased prevalence of GI lesions, which are detectable on bidirectional endoscopy. The results of the study suggest that all young men with IDA should be evaluated with endoscopies & specific complaints may dictate the order of evaluation. Men with prominent symptoms of heartburn or epigastric pain can start their evaluation with UGIE, while colonoscopy should be the initial evaluation in men with lower GI symptoms. Celiac serology (IgA TTG) should be performed in all such cases, regardless of symptoms, as the disease is present in our population and is amenable to therapy. In patients with IDA, those with low serum ferritin, positive GI symptoms, and positive fecal occult blood test, are more likely to have potentially correctable GI lesions on endoscopies.The findings of this study with a small sample size (N=50), need further validation with a larger multi-centric study.

Conflict of interest – Nil

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