



Anemia in patients with ulcerative colitis in remission: A study from western India

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Abstract

Background Anemia is common in patients with active ulcerative colitis. We aimed to study the anemia profile in patients with ulcerative colitis in clinical remission.

Methods Sixty-four patients with ulcerative colitis and with a clinical Mayo score less than 3 for at least 3 months were evaluated for anemia. Initial screening was done by hemogram and only patients with anemia were evaluated further for the cause of anemia. We also screened a control population for anemia. Patients with mild anemia were given oral iron, moderate anemia were given intravenous iron and severe anemia were given blood transfusion.

Results The mean hemoglobin in ulcerative colitis patients was 11.75 g/dL and in controls was 13.1 g/dL ($p=0.011$). The prevalence of anemia was 53.1% in the ulcerative colitis patients and 13.3% in the controls ($p<0.001$). 58.8% had mild anemia, 29.4% had moderate anemia and 8.8% had severe anemia. Iron deficiency was the most common cause of anemia (70.5%) followed by anemia of chronic disease combined with iron deficiency in 23.5%. Ferritin levels did not correlate with hemoglobin levels. Oral iron increased the hemoglobin by 1.4 g/dL and intravenous iron by 2.2 g/dL at 1 month.

Conclusion Anemia was seen in more than half of patients with ulcerative colitis in clinical remission, iron deficiency being the most common cause.

Keywords Anemia · Iron deficiency · Iron preparations · Remission · Ulcerative colitis

Introduction

Anemia is a major cause of morbidity in patients with ulcerative colitis causing symptoms of easy fatigability, sleeping disorders, restless legs syndrome, attention deficit and female infertility impairing the quality of life [1, 2]. It is seen in almost two thirds of the patients with ulcerative colitis the major causes being iron deficiency due to blood loss, anemia of chronic disease and other causes such as nutritional deficiency, medication use and other causes of anemia as seen in the general population [3]. Our study included patients with ulcerative colitis who were in remission for at least 3 months and had a C-reactive protein level within normal limits. We aimed to study the anemia profile in these patients and hemoglobin response to iron therapy.

Methods

It was a single centre observational study with data collected over a period of 1 year from October 2015 up to October 2016. The study was approved by the Ethics committee of the institute. Patients who were previously diagnosed with ulcerative colitis and were in clinical remission, i.e. had a clinical Mayo score less than 3 with no rectal bleeding and a normal C-reactive protein level (<6 mg/dL), were included in the study. Informed consent of the patients was taken. A total of 64 patients with ulcerative colitis meeting the above criteria were included. A control population of 30 patients with functional dyspepsia were evaluated for the incidence of anemia in the general population. These patients were outpatients at a

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municipal hospital and belonged to the same socioeconomic class (lower, lower middle) as the patients with ulcerative colitis. A detailed drug history was taken. Disease extent as per previous colonoscopy was noted. Patients taking hematinics were not included in the study. WHO classification for anemia was used and a cut off hemoglobin (Hb) level of 12 g/dL for females and 13 g/dL for males was used. Only patients who had anemia were investigated further. A diagnostic algorithm for investigation was followed. The tier 1 investigations were mean corpuscular volume (MCV), red cell distribution width (RDW) and corrected reticulocyte count. The normal levels for MCV were 80–95 femtolitre (fL), RDW were 11.5% to 14.5% and corrected reticulocyte count were 0.5% to 1.5%. Patients with low/normal MCV, low/normal reticulocyte count and high RDW were evaluated for iron deficiency. The tier 2 investigations were serum ferritin and transferrin saturation for these patients. Normal ferritin levels were 30–300 microgram per litre (mcg/L) and transferrin saturation was 15% to 50%. Patients with transferrin saturation less than 20% and ferritin levels less than 30 mcg/L have iron deficiency anemia, between 30 and 100 mcg/L have combined iron deficiency and anemia of chronic disease and > 100 mcg/L have anemia of chronic disease with functional iron deficiency. Other causes of anemia like menorrhagia were ruled out. Stool examination was done to exclude parasitic infestation. Upper GI scopy with duodenal biopsy done to rule out malabsorption in patients who did not have adequate response to oral iron or who had moderate to severe anemia (Hb <10 g/dL). Those found to be iron deficient were subjected to flexible sigmoidoscopy to assess for disease activity. Patients with Hb less than 7 were given blood transfusions. Patients with moderate iron deficiency anemia (Hb between 7 and 10 g/dL), intolerant of oral iron, were given intravenous ferric carboxymaltose (500 mg single dose repeated weekly, 1500 mg—<70 kg body weight and 2000 mg—>70 kg body weight) [4]. Patients with Hb >10 g/dL were given oral iron (325 mg ferrous sulphate containing, 65 mg elemental iron, 1 tablet twice daily). Hemoglobin levels were repeated after 1 month of iron replenishment therapy. An increase of hemoglobin by 2 g/dL was considered adequate response.

Patients with low MCV and a high reticulocyte count were investigated for hemolysis by lactate dehydrogenase, peripheral smear, Hb electrophoresis and osmotic fragility. Patients with high MCV were evaluated for vitamin B₁₂, folate deficiency. If no cause was found bone marrow examination was done.

Statistical analysis

P-values of < 0.05 were considered to be statistically significant. Prevalence of anemia was compared between ulcerative colitis patients and controls using chi-square tests.

Hemoglobin values between the two groups were compared using Student's unpaired *t* test. Correlation between anemia and ferritin levels was assessed using logistic regression.

Results

Patient characteristics (Table 1)

Out of 64 patients with ulcerative colitis, 35 were males and 29 were females. The control group had 30 patients with 15 males and 15 females. Thirty-nine out of the 64 patients (61%) were taking azathioprine whereas 22 patients were maintained on mesalamine. Biologicals or methotrexate was not given to any of the patients. The mean hemoglobin in ulcerative colitis patients was 11.75 g/dL and controls was 13.1 g/dL (*p*=0.011). The mean hemoglobin for males was 12.26 g/dL in ulcerative colitis patients and 14.2 g/dL in controls (*p*=0.001). The mean hemoglobin for females was 10.97 g/dL in ulcerative colitis patients and 12.8 g/dL in controls (*p*<0.00). The MCV in ulcerative colitis patients was 81.8 fL for males and for females was 77.71 fL.

Anemia (Table 2)

The prevalence of anemia was 53.1% in the ulcerative colitis patients and 13.3% in the controls (*p* = <0.001). In the ulcerative colitis patients having anemia, 58.8% had mild anemia, 29.4% had moderate anemia and 8.8% had severe anemia. The prevalence of anemia in males was 51.4% in ulcerative colitis patients as compared to 6.7% in the control group (*p*=<0.001). In the male ulcerative colitis patients having anemia, 55.5% had mild anemia and 45.5% had moderate anemia. The prevalence of anemia in females was 55.1% in ulcerative colitis patients as compared to 20% in the control group. In the female ulcerative colitis patients having anemia, 68.75% had mild anemia, 12.5% had moderate anemia and 18.75% had severe anemia.

Mean corpuscular volume

Fifty percent of ulcerative patients had microcytic anemia, 41.18% had normocytic anemia and 8.82% had macrocytic anemia.

Serum ferritin (Table 3)

Serum ferritin levels were less than 30 in 70.5% of ulcerative colitis patients, between 30 and 100 in 26.4% patients and more than 100 in 2.9% patients. In the male patients with ulcerative colitis, serum ferritin levels were less than 30 in 55.56% of ulcerative colitis patients, between 30 and 100 in 38.89% patients and more than 100 in 5.55% patients. In the

Table 1 Hemoglobin and erythrocyte indices in the study groups

	Mean Hb (g/dL)	Mean MCV (fL)	Mean RDW (%)
All patients (ulcerative colitis) (<i>n</i> =64)	11.75	81.8	18.2
Males (ulcerative colitis) (<i>n</i> =35)	12.26	84.51	17.7
Females (ulcerative colitis) (<i>n</i> =29)	10.97	77.71	21.8
Controls (<i>n</i> =30)	13.1	84.1	14.4
Males (controls) (<i>n</i> =15)	14.2	87.8	12.4
Females (controls) (<i>n</i> =15)	12.2	80.4	16.4

MCV mean corpuscular volume, RDW red cell distribution width

female patients with ulcerative colitis, serum ferritin levels were less than 30 in 87.5% of ulcerative colitis patients and between 30 and 100 in 12.5% patients. Among the controls, 2 females had a ferritin level less than 30.

True iron deficiency

Serum ferritin of less than 30 with transferrin saturation less than 20% was seen in 70.5% patients of ulcerative colitis patients with anemia with a prevalence of 55.55% (10/18) in males and 87.5% (14/16) in females.

Iron deficiency with anemia of chronic disease

Serum ferritin between 30 and 100 with transferrin saturation less than 20% was seen in 23.5% (8/34) patients of ulcerative colitis patients with anemia with a prevalence of 33.33% (6/18) in males and 12.5% (2/16) in females.

Extent of disease

Extent of disease (Montreal classification) as determined by previous colonoscopy was noted in all patients enrolled for the study. Anemia was seen in 100% of patients with pancolitis (22/22) and 20.8% of patients with left sided colitis (10/48).

Causes of anemia according to prevalence in ulcerative colitis patients (Table 4)

Iron deficiency was found to be the sole cause of anemia in 70.5% ulcerative colitis patients with a prevalence of 55.5% in males and 87.5% in females. Iron deficiency with anemia of chronic disease was found in 26.4% ulcerative colitis patients with a prevalence of 38.9% in males and 11.1% in females. Anemia of chronic disease was found in 2.95% patients with a prevalence of 5.55% in males. Vitamin B₁₂ deficiency was found in 8.82% patients overall with a prevalence of 5.55% male patients and 12.5% female patients. Drug-induced anemia (patients receiving thiopurine) was found in 5.8% patients with a prevalence of 12.5% in females. A single female patient was found to be positive for thalassemia trait.

Treatment response

Thirty-three out of 34 patients with anemia had iron deficiency. Three patients had severe anemia and were advised blood transfusion. Ten patients had moderate anemia and were advised to take intravenous iron. However, five patients refused to give consent for intravenous iron and were given oral iron. Three patients were not able to tolerate oral iron. One patient had dysphagia; two patients had exacerbation of disease process and were excluded from the treatment group. So six

Table 2 Prevalence and severity of anemia in the study groups

	Hb <12 females Hb <13 males	Mild (10–12 g/dL females) (10–13 g/dL males)	Moderate (8–10 g/dL)	Severe < 8 g/dL
Overall (UC)	34/64 (53.1%)	20/34 (58.8%)	10/34 (29.4%)	3/34 (8.8%)
Males (UC)	18/35 (51.4%)	10/18 (55.5%)	8/18 (44.5%)	0
Females (UC)	16/29 (55.1%)	11/16 (68.75%)	2/16 (12.5%)	3/16 (18.75%)
Controls (C)	4/30 (13.3%)	2/30 (6.7%)	2/30 (6.7%)	
Males (C)	1/15 (6.7%)	1/15 (6.7%)		
Females (C)	3/15 (20%)	1/15 (6.7%)	2/15 (13.33%)	

UC ulcerative colitis

Table 3 Ferritin levels and iron deficiency in the study groups

	Mean (mcg/L)	< 30 mcg/L	30–100 mcg/L	> 100 mcg/L
Overall	42.9	24/34 (70.5%)	9/34 (26.4%)	1/34 (2.9%)
Males	33.58	10/18 (55.56%)	7/18 (38.89%)	1/18(5.55%)
Females	18.67	14/16 (87.5%)	2/16 (12.5%)	0
Controls	90.4	2/4 (50%)	0	2/4 (50%)
Males	112.6			1/4 (25%)
Females	68.2	2/4 (50%)		1/4 (25%)

patients were given intravenous iron. The increase in serum hemoglobin was 1.4 g/dL for patients given oral iron and 2.2 g/dL for those given intravenous iron at 1 month. Twenty percent (4/25) of the patients with iron deficiency did not have adequate response to oral iron whereas 100% (6/6) patients had adequate response to intravenous iron. One patient with inadequate response and 1 patient with severe anemia were found to have celiac disease by serology (IgA TTG–tissue transglutaminase) and duodenal biopsy.

Discussion

Anemia in ulcerative colitis has been attributed to chronic blood loss, anemia of chronic disease, vitamin B₁₂ deficiency secondary to terminal ileitis, folate deficiency due to sulfasalazine therapy or azathioprine induced [2]. Anemia can result in symptoms like chronic fatigue impairing the quality of life [1]. We chose a study group of patients having ulcerative colitis patients who were in clinical remission because these were the patients in whom anemia would go unrecognised unless specifically tested for. The WHO criteria were used for defining anemia with a cut off hemoglobin value of 12 g/dL in females and 13 g/dL in males. In a systematic review, Gisbert and Gomollon found the prevalence of anemia in patients with inflammatory bowel disease (IBD) to range from 16% to 74%, with a mean value of 16% in outpatients and 68% in hospitalized patients [5]. In our study,

53.1% patients had anemia as compared to the control population where 13.3% had anemia. Of these, 8.8% had severe anemia, 29.4% had moderate anemia and 58.8% had mild anemia. The occurrence of overt symptoms in patients with mild anemia who constitute the majority is minimal and hence this group would escape investigation and treatment. A recent study in veterans found that more than a third of anemic ulcerative colitis patients were not tested for iron deficiency and almost a quarter of the patients with iron deficiency anemia were not treated with iron replacement therapy [6]. A low reticulocyte count and high RDW indicates nutritional deficiency. Microcytosis suggests iron deficiency, macrocytosis suggests vitamin B₁₂/folate deficiency and normocytosis suggests a mixed picture. Evaluation for iron deficiency has been debated upon with suggestions for new markers such as soluble transferrin receptor, sTfR/log ferritin index and red blood cell size factor [7, 8]; sTfR/log ferritin index <1 excludes iron deficiency and suggests anemia of chronic disease [9]. However, the new markers are costly and not readily available. Ferritin being an acute phase reactant could give false negative values in the presence of inflammation. Hence, in our study, we ruled out laboratory (CRP, leukocyte count) and clinical evidence of inflammation (stool frequency <3 with no blood) and used levels of ferritin <30 mcg/L to define iron deficiency. The diagnostic criteria for anemia of chronic disease were serum ferritin >100 µg/L and transferrin saturation <20%. If the serum ferritin level is between 30 and 100 µg/L and transferrin saturation <20%, a combination of

Table 4 Distribution of anemia by cause

Cause of anemia	Prevalence overall <i>n</i> (%)	Prevalence in males <i>n</i> (%)	Prevalence in females <i>n</i> (%)
Iron deficiency	24 (70.5)	10 (55.5)	14 (87.5)
Iron deficiency+anemia of chronic disease	9 (26.4)	7 (38.8)	2 (11.1)
Anemia of chronic disease	1 (2.9)	1 (5.5)	0
Vitamin B ₁₂ deficiency	3 (8.8)	1 (5.5)	2 (12.5)
Celiac disease	2 (14.3)	1 (11.1)	1 (20)
Drug-induced anemia	2 (5.8)	0	2 (12.5)
Thalassemia trait	1 (2.9)	0	1 (6.2)

true iron deficiency and anemia of chronic disease is present [10]. These patients were subjected to flexible sigmoidoscopy to look for endoscopic inflammation. In our study, we found iron deficiency to be the most common cause of anemia (70.5%). Anemia of chronic disease combined with iron deficiency was seen in 23.5%. This was similar to anemia found at the time of diagnosis of ulcerative colitis as per another study, implying that patients with ulcerative colitis have occult gastrointestinal blood loss/nutritional deficiency and require iron supplementation and even modification of treatment [11]; 55.1% females had anemia as compared to 51.4% males. Serum ferritin levels were <30 mcg/L in 87.5% of females and 55.65% males. Ferritin levels did not correlate with hemoglobin levels. Anemia was seen in 100% of patients with pancolitis (22/22) and 20.8% of patients with left sided colitis (10/48) as per extent determined by previous colonoscopy.

An increase in hemoglobin of at least 2 g/dL within 4 weeks of treatment is an acceptable speed of response [12]. Recent studies show that intravenous iron has better tolerability and higher efficacy than oral iron [13, 14]. Preparations such as iron sucrose, ferric carboxymaltose, iron isomaltoside and more recently ferumoxytol have been used. We used ferric carboxymaltose in our study. We found that those receiving intravenous iron had a higher hemoglobin increase than oral iron. However, patient willingness for injectable iron treatment was low and oral iron was well tolerated by most patients. Hence, we conclude that the patients of ulcerative colitis who are treated for iron deficiency are only a tip of the iceberg and a majority of patients with quiescent disease have underlying iron deficiency. These patients should be identified and can be screened by an easily available investigation like a hemogram and there iron deficiency can be corrected in a cost effective manner.

Vitamin B₁₂ deficiency was found in three patients of which two consumed a pure vegetarian diet and one patient had pernicious anemia. Two patients on azathioprine had anemia in which no other cause could be found. Two patients were found to have coexistent celiac disease. The limitation of our study was that malabsorption was ruled out in a subset of patients who had moderate to severe anemia and those who did not respond adequately to iron therapy.

Iron deficiency anemia persists in a significant proportion of patients with ulcerative colitis in remission and needs to be treated appropriately.

Compliance with ethical standards Procedures performed were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Conflict of interest AC, VP, DC, PP, MI, AP, and PS declare that they have no conflict of interest.

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