Prevalence and treatment of anemia in inflammatory bowel disease in a Colombian reference center

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Abstract

Introduction: Anemia is the most frequent complication of inflammatory bowel disease (IBD). This study aims to determine the prevalence, connection, and treatment of anemia in IBD in a local context. Materials and Methods: This retrospective study was conducted at The Pablo Tobon Uribe Hospital, in Medellín (Colombia) with adult patients who (were admitted) came for consultation from 2001, until February 2019. Absolut and relative frequencies were calculated. The Chi square test of independence was applied for comparing two proportions and the odds ratio (OR) was estimated. Results: A total of 759 IBD patients were enrolled, 544 (71.6%) with ulcerative colitis (UC); 200 (26.3%) Crohn’s disease (CD), and 15 (1.9%) with non-classifiable IBD. In total, 185 (24.4 %) IBD patients had a diagnosis of anemia, that is less frequent in UC patients that in CD patients (22.2 % versus 32.5 %, respectively; OR: 0.684; CI: 0.456-0.96; p = 0,03). Extensive UC patients (54,1 %) had a more recurrent level of anemia than non-extensive UC (46,3 %) (OR: 4,95; CI: 2,87-8,51; p = 0,001); the same result was observed when severe UC (66,1 %) was compared with UC non-severe (32,3 %) (OR: 4,95; CI: 2,87-8,51; p = 0,000). In the analysis of CD, patients with a non-inflammatory response (B1, B3: 73,9 %) had a more recurrent level of anemia than patients with an inflammatory response (B1: 26,2 %) (OR: 0,35; CI: 0,18-0,67; p = 0,000). 44,3 % of the total number of patients received treatment, 19,5 % received oral iron, 20,0 % received intravenous iron, and 16,2 % received a blood transfusion. Conclusions: In our context, Anemia is a common complication in IBD cases (24,4 %). Despite the existence of international guidelines, the treatment in our context is not optimal. Keywords Anemia; Inflammatory Bowel Disease; Prevalence; Parenteral Iron.

INTRODUCTION

Anemia is the most common complication of inflammatory bowel disease (IBD) (1). It is associated with a more disabling disease (2) with a significant impact on the quality of life (3,4) and has historically received little attention from gastroenterologists (5). Anemia is defined by the World Health Organization (WHO) as hemoglobin (Hb) levels < 12 g/dL in non-pregnant women and < 13 g/dL in men (6). The European Crohn’s and Colitis Organisation (ECCO) adopted the previous definition of anemia in a recent consensus, which recommends ruling out this complication in all individuals with IBD (1).

The etiology of anemia in IBD is multifactorial. The most common causes are iron deficiency anemia (IDA) and anemia of chronic disease (ACD), which can coexist (mixed); other causes of anemia such as those associated with vitamin B12 or folic acid deficiency, or induced by drugs are less frequent (7,8). In a systematic review of 17 articles with CD, the prevalence ranges between 4% and 67% (9). Gisbert et al reported a 17% average prevalence of anemia in IBD, and figures of 16% were found in outpatients and 68% in hospitalized indi-
IBD prevalence in Latin America is increasing, and there is little data on the relationship between anemia and IBD. Two studies in Brazil found a prevalence of anemia of 21% and 24.6% in patients with IBD. This study aims to determine the prevalence, associations, and treatment of anemia in a cohort of IBD patients in our center.

**MATERIALS AND METHODS**

The diagnoses of ulcerative colitis (UC) and Crohn’s disease (CD) were searched in the clinical records of the Hospital Pablo Tobón Uribe in Medellín, Colombia, until February 2019, considering the following codes: K500 CD of the small intestine, K501 CD of the large intestine, K508 other types of CD, K509 CD unspecified, K519 UC unspecified, and K518 other UCs. Data from adult patients with UC and CD, who attended the emergency department, were hospitalized, or were served by the outpatient clinic, were retrospectively analyzed to determine the prevalence of anemia.

**Definitions of anemia**

Anemia was diagnosed in patients with Hb levels < 12 g/dL for non-pregnant women and < 13 g/dL for men, according to the WHO recommendation. IDA was considered at ferritin levels < 30 mg/L and normal C-reactive protein (CRP) levels, or in the case of ferritin < 100 mg/L and high CRP, but with a transferrin saturation percentage < 16%. ACD was defined as normal or elevated ferritin levels, normal average transferrin saturation percentage, and elevated CRP. Anemia due to deficiencies of vitamin B12 (< 211 ng/mL) and folic acid (< 7 ng/mL) were defined when the levels were below the average level. Other measurements such as mean corpuscular volume (MCV), red blood cell distribution width (RDW), and percentage of reticulocytes were also incorporated to classify anemia. Patients in whom anemia could not be defined due to insufficient data were excluded from the study.

Mild anemia refers to Hb levels of 11.0–11.9 g/dL in women and 11.0–12.9 in men, moderate 8.0–10.9 g/dL, and severe with levels < 8 g/dL, according to WHO recommendations. UC activity was defined by the Truelove and Witts classification, considering the activity at the time of the most severe episode of UC for the analysis. According to the Montreal Classification, the extent of UC was defined. The location and behavior of the CD were determined by the Montreal Classification.

**Data collection**

A database with Excel format was built, collecting the following data from each patient for analysis:

- Type of IBD (UC, CD, and IBD not classifiable)
- Sex of the patient
- Anatomical extension of the UC
- UC activity
- Location of CD
- CD behavior
- Cumulative medical treatment (5-aminosalicylic acid [5-ASA], steroids, immunosuppressants, biological therapy)
- Surgical treatment
- Hospitalization rate
- Presence of anemia
- Type of anemia
- Severity of anemia
- Treatment of anemia

The following measurements were considered to classify anemia: Hb, hematocrit, MCV, serum ferritin, percentage of transferrin saturation, and CRP. In patients with elevated MCV, we verified vitamin B12 and folic acid levels.

**Statistical analysis**

Absolute and relative frequencies were used for qualitative variables, and mean, standard deviation (SD), or median and interquartile range (IQR; P25–P75) were used for quantitative variables after verifying the assumption of normality with the Kolmogorov-Smirnov tests. The chi-square test (χ²) of independence was employed to compare two proportions, estimating the odds ratio (OR) with its appropriate 95% confidence interval (CI).

**Ethical considerations**

In this risk-free research, the patients’ medical records were reviewed, ensuring the confidentiality and privacy of the information collected. The project researchers adhered to the international principles of the 2013 Declaration of Helsinki in Fortaleza, Brazil, and Articles 10 and 11 of Resolution 008430/1993 issued by the Ministry of National Health of Colombia.

**RESULTS**

In this retrospective, descriptive, analytical study, 759 patients who met diagnostic criteria for IBD were systematically included, of which 544 (71.6%) had a diagnosis of UC, 200 (26.3%) of CD, and 15 (1.9%) of unclassifiable IBD. Anemia was documented in 185 of the 759 patients (24.4%) with IBD. In UC, 121 of 544 (22.2%) had anemia, compared with 65 of 200 patients (32.5%) with CD (OR: 0.684; CI: 0.456–0.96; p = 0.03). Regarding severe anemia,
hospitalization compared to those without anemia (59.5% vs 47.0%; OR: 1.95; CI: 1.37–2.77; \( p = 0.000 \)); this was not demonstrated in individuals with CD (72.3% vs 63.0%, OR: 1.14; CI: 0.72–1.82; \( p = 0.63 \)) (Table 1).

For the treatment of anemia and IBD, 82 of 185 (44.3%) patients with anemia did not receive treatment, 19.5% received oral iron, 20.0% intravenous (IV) iron, and 16.2% a transfusion (Figure 2). In the subgroup of patients with severe anemia, 24 of 87 (27.6%) were untreated, 12.6% received oral iron, 29.9% received IV iron, and 29.9% had a transfusion. No patient received erythropoietin.

### DISCUSSION

The prevalence of anemia in 759 adult patients with IBD, both outpatient and hospitalized, in our center is high (24.4%), and it is more frequent in CD (32.5%) than in UC (22.2%), as reported in the universal literature. A European meta-analysis with 2,192 patients found a prevalence of anemia in 24% of cases with IBD, 27% of cases with CD, and 21% of cases with UC.(19) The Norwegian IBSEN group also identified a higher proportion of anemia at diagnosis in CD (48.8%), compared to UC (20.2%).(19) A Swedish study found 30% anemia in IBD patients at diagnosis, 42% in CD patients, and 24% in UC patients.(20) A more recent publication from the University of Pittsburgh detected a prevalence of anemia in patients with IBD of 33.2%, 34.3% in patients with CD, and 31.5% in patients with UC.(2) The ECCO-EPICOM cohort study noticed a higher prevalence of anemia in patients with CD of 49% and 39% in patients with UC during the first year after diagnosis.(21)

The high number of patients with severe anemia in our IBD patients (40.0%), compared with other series, was striking. In a multicenter study in nine European countries with 1,404 patients with IBD, 56% of individuals with at least moderate anemia (Hb <10 g/dL) were observed, but only 15% had severe anemia. The severity of anemia was mild in 76.2%, moderate in 15%, and severe in 8.8% in a report of 193 cases associated with IBD in 55 centers in Germany.(23) It can be explained by the severity of patients with IBD who are cared for in our tertiary referral center. These two series are surveys of the participants, with no analysis of IBD severity in their patients.

On the one hand, our study demonstrated a predominance of IDA (55%) and mixed (41%) over other etiologies of anemia. In a Scandinavian study,(24) the etiology of anemia in IBD was IDA (20%), ACD (12%), mixed (68%), and a deficiency of vitamin \( B_{12} \) and folic acid (5%). As found in our study, but with a higher proportion of mixed anemia.

On the other hand, in our study, patients with UC and anemia presented with more strenuous activity (S3), more significant anatomical extension, and more disabling
disease due to a higher hospitalization rate and greater use of biological therapy. In individuals with CD, anemia was associated with non-inflammatory behavior (stenosing or penetrating), so these patients are more complicated and have a worse prognosis than patients with inflammatory behavior. In the ECCO-EPICOM study already mentioned, patients with extensive UC and penetrating CD had a higher risk of anemia, just like in this study\(^{(21)}\). In the Swedish study, anemia was also associated with extensive UC\(^{(20)}\). Data from the University of Pittsburgh study above also show a significant correlation of anemia with higher rates of disease activity and hospitalization\(^{(2)}\).

The ECCO guidelines\(^{(1)}\) recommend using oral iron in IBD patients with mild IDA defined by the WHO with Hb levels of 11–11.9 g/dL, whose IBD is clinically inactive and with good tolerance to the drug. IV iron should be considered as the first line of treatment in patients with intolerance to oral iron, active IBD, Hb levels < 10 g/dL, and in patients requiring erythropoietin\(^{(1)}\). A recent review article, considering the 2019 coronavirus disease pande-

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<th>Table 1. Clinical features of IBD and anemia</th>
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<td><strong>Patients (n)</strong></td>
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<td><strong>Anemia</strong></td>
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<td><strong>No anemia</strong></td>
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<td><strong>UC extension</strong></td>
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<td>- E1: proctitis + E2: left</td>
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<td>- E3: extensive colitis</td>
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<td><strong>CD location</strong></td>
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<td>- L1: terminal ileum</td>
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<td>- L3: terminal ileum + colon</td>
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<td>- L4: upper GI</td>
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<td>- L2: colon</td>
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<td><strong>Severity of UC symptoms</strong></td>
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<td>- Non-severe activity (S1 + S2)</td>
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<td>- Severe activity (S3)</td>
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<td><strong>Behavior of CD</strong></td>
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<td>- B1: inflammatory</td>
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<td>- B2 + B3 + P</td>
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<td><strong>Biological/surgery/hospitalization for UC</strong></td>
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A global survey of patients with anemia and IBD found that 33% reported not receiving treatment for their anemia. Of those treated, 52% received oral iron, 27% IV iron, and 19% other types of supplements. Of the patients with oral iron, 74% were not satisfied with the treatment, while 72% were satisfied with IV iron.

The Crohn’s & Colitis Foundation of America (CCFA) recently appointed a committee of experts to make recommendations and develop an algorithm for the screening, evaluation, intervention, and follow-up of patients with anemia and IBD. A later publication assessed adherence to these recommendations and found that iron therapy in anemic patients increased from 30% to 80%, and the prevalence of anemia decreased from 48% to 25%. However, the percentage of iron deficiency screening did not change; only 20% of anemic patients underwent a ferritin measurement.

A recent review article recommends a treat-to-target approach for patients with IDA associated with IBD, as proposed for the treatment of IBD, divided into three steps: early detection, treat-to-target (normalization of Hb and iron stores), and strict monitoring (ferritin and transferrin saturation percentage every 3–6 months) due to the high risk of recurrence.

Within the limitations of this study, it may contain interpretation biases, as it is a retrospective study based on data collected from the medical records. Additionally, this study was carried out in a tertiary referral hospital, a reference center for IBD patients throughout the country, with probably more severe and complicated patients than those from other centers in the country.
CONCLUSIONS

There is a high prevalence of anemia associated with IBD in our setting, which is more frequent in CD than in UC, consistent with other studies worldwide. It could be explained by insufficient diagnosis, ineffective treatment, and a lack of monitoring of these individuals with anemia. Anemia in patients with IBD is associated with greater severity of the disease. Additionally, the preferred route of administration of iron in IDA, both in this and other series cited, is oral, regardless of the severity of the anemia, the high percentage of intolerance to oral iron, and international guidelines. It is necessary to become more aware of this complication in patients with IBD and make more efforts in medical education to implement guideline recommendations and apply them to the early diagnosis, adequate management, and monitoring of these individuals. Nonetheless, the most important thing will always be the timely and adequate treatment of IBD to prevent this complication. A proposal for the management of anemia in patients with IBD is presented in Figure 3.

Conflicts of interest

None of the study authors reported conflicts of interest.

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Author contribution

F. Juliao-Baños participated in the study design, recruitment of patients, and writing of the paper. M. Arrubla, L. Osorio, J. Camargo, J. Londoño, and C. Cáceres carried out the data collection. J. Carvajal, G. Mosquera, and A. Gomez participated in the recruitment of patients. J. Donado performed the statistical analysis.

Figure 3. Anemia management algorithm in IBD. TS: Transferrin saturation.
REFERENCES


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