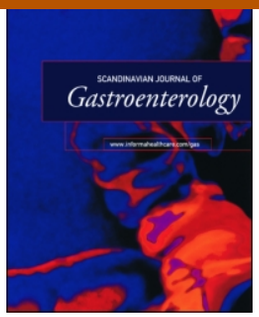

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ORIGINAL ARTICLE

Prevalence of iron deficiency anemia and iron deficiency in a pediatric population with inflammatory bowel disease

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ABSTRACT

Objectives: Iron deficiency is the most common cause of anemia in children with inflammatory bowel disease, although the real prevalence is unknown. Intravenous iron is suggested as the first line treatment. This study aims to determine the prevalence of iron deficiency anemia in children with inflammatory bowel disease followed in a Pediatric Gastroenterology Unit of a tertiary center and to evaluate this unit's experience with intravenous iron.

Materials and methods: A retrospective cohort study was designed involving children with inflammatory bowel disease followed in that unit between January 2001 and April 2016. Laboratory results were collected at the moment of diagnosis, after one-year follow-up and prior each IV iron administration performed during the study period. Anemia was defined according to World Health Organization criteria and the iron deficiency was defined using recent guidelines.

Results: Were studied 69 patients 71% had CD and 29% UC. 50.7% were female. Mean patient age at diagnosis was 13.3 years (range 1–17 years). Prevalence of ID and IDA at diagnosis was 76.8% and 43.5%, respectively. After one year follow-up, those values decreased to 68.1% ($p = .182$) and 21.7% ($p = .002$), respectively. Hemoglobin significantly increased ($p < .001$). Intravenous iron was administered to 92.8% of patients. No adverse reactions were reported.

Conclusions: Intravenous iron is the first line in the treatment of Iron deficiency anemia in Inflammatory Bowel disease and it is safe and effective. Persistent anemia and iron deficiency are common.

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Iron deficiency; iron deficiency anemia; intravenous iron; inflammatory bowel disease; pediatrics

Introduction

Anemia is the most common systemic complication of inflammatory bowel disease (IBD) [1]. The etiology is multifactorial, but in 80% of cases it results due to the combination of iron deficiency anemia (IDA) and anemia of chronic disease (ACD) [2–4]. The true prevalence of iron deficiency (ID) and IDA in the pediatric population is unknown. In recent studies, Goodhand *et al.* and later Danko estimated it to be up to 70% at diagnosis and even after two years of follow-up prevalence can be as high as 30% [2,4–10].

ID has an adverse impact on quality of life [6,9,11,12]. Therefore, it is important to carefully evaluate iron status of all patients so that ID and IDA can be diagnosed and treated timely [7,8].

Studies on ID and IDA in children are scarce and difficult to compare because most times different cut-off values are used to define anemia and the interpretation of iron indices must take into account inflammation parameters. In context of IBD, interpreting serum ferritin relative to C-reactive protein has been proposed as a method to detect iron deficiency [2,8,9].

Oral iron was once the standard treatment of IDA and ID. Recently, its gastrointestinal side-effects, slow onset of action and negative impact on disease activity gave rise to the use of intravenous formulations [2,5,6,9,13–15]. There have been some concerns regarding the safety of these preparations in the pediatric population, mainly with dextran formulations which carry increased risk of anaphylaxis [6,8,9,15,16]. But, now, the new formulas such as iron sucrose and ferric carboxymaltose (FCM), the last one still only approved for patients over 14 years, have better safety profiles and are now the first line treatment for IDA and ID in IBD patients [3,4,8,9,16–18].

There are few studies that estimate the prevalence of ID and IDA in pediatric IBD patients and even fewer that evaluate the efficacy of intravenous iron to treat them [1,4,5]. Thus, the aim of this study was to calculate the prevalence of ID and IDA in children with IBD followed in a Pediatric Gastroenterology Unit and evaluate this unit's experience in their treatment with IV iron.

Materials and methods

Study sample, design and approval

A retrospective cohort study was conducted in the Gastroenterology, Hepatology and Nutrition Unit of the

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Pediatrics Department of Hospital de Braga, a tertiary unit that serves the region of Minho. The primary objective of this study was to evaluate the changes in ID and IDA's prevalence after the first-year of diagnosis. In order to do that, we determine the prevalence of ID and IDA at the moment of diagnosis and after the first-year of follow-up. A secondary objective of this study was to evaluate this unit's experience with intravenous iron therapy in the last 15 years.

All pediatric patients (under 18 years) diagnosed with IBD and followed in that unit between January 2001 and April 2016 were selected and their electronic health record reviewed. Patients with an incomplete electronic health record, who have not completed one-year follow-up, with hemoglobinopathies and history of previous blood transfusions were excluded. All data collected, as well as the study design, were approved by the institutional review board and ethics committee. Patient identities were protected during the study.

Study variables

All data were collected from the electronic health record and included demographic information (actual age, gender, age at diagnosis), medical history and status of patient's IBD at diagnosis. Prevalence of ID and IDA was obtained by studying hemoglobin (Hb), C-reactive protein (CRP) and ferritin values at diagnosis and after one-year follow-up. To evaluate the unit's experience with IV iron therapy, all IV iron administrations that took place in that unit during the 15 years studied were analyzed. Laboratory values prior to each IV iron administration, such as Hb, CRP, ferritin, mean corpuscular volume (MCV) and hematocrit (Ht) were analyzed, and all adverse reactions and the iron cumulative dose administered to each patient during their first year follow-up and during their entire follow-up in the Unit were registered.

Definitions of Disease Activity, Anemia and Iron Deficiency

Anemia was defined according to World Health Organization cut-offs for Hb concentration specific to age groups and gender: under 5 years, anemia was defined as Hb concentration under 110g/L, between 5 and 11 years Hb under 115g/L, between 12 and 14 years under 120g/L, non-pregnant girls over 15 years under 120g/L and boys over 13 years under 130g/L. ID was defined as serum ferritin $<30\mu g/L$ when CRP $<10mg/L$ and serum ferritin $<100\,\mu g/L$ when there was evidence of inflammation (CRP $>10mg/L$). In our group, we elected these criteria since it takes into account the fact that ferritin can be altered by inflammation itself.

Disease activity was defined according to PCDAI index and CRP values in Crohn's disease (CD) and PUCAI index and clinical features were used to divide Ulcerative Colitis (UC) patients in mild, moderate and severe.

Intravenous iron treatment

IV iron was used as the first line in treatment of ID and IDA; oral iron was prescribed only when the patient refused IV administration. The IV iron deficit was calculated according to the Ganzoni formula [Weight (kg) × (target Hb- real Hb g/dlx0.24) + iron stores (>35 kg: 500 mg, < 35 kg: 15 mg/kg)] [19]. The maximum single dose allowed per infusion was 200 mg per day. When deficit was superior, the patient was submitted to several infusions in consecutive days. After the successful treatment of IDA or ID with IV iron, it was reinitiated as soon as the serum ferritin level dropped, which was determined every three to six months according to disease's activity. The variable 'treatment' was defined as the total number of infusions needed to treat or prevent ferropenia. All patients submitted to IV iron therapy received iron sucrose. Adverse side effects were considered within the first 24h after iron administration.

Statistical analysis

Statistical analysis was performed using SPSS® 21.0 (Chicago, IL). Laboratory values were expressed as mean. Changes in CRP, ferritin, Hb values and in the prevalence of anemia, IDA and ID from diagnosis to one-year follow-up were evaluated using a paired *t*-test. All *p*-values are 2-sided and $p < .05$ was used to define statistical significance.

Pearson's correlation was used to determine associations between disease severity and Hb values and between disease severity and cumulative iron dose. Correlation between age at diagnosis and the cumulative iron dose was also studied using a level of significance of .01.

Results

During the study period, 100 patients were diagnosed with IBD, 16 were excluded because their electronic health record was incomplete and 15 were excluded because they have not completed one-year follow-up. From the remaining 69 patients included in the study, 71% (49) had CD and 29% (20) UC. 50.7% were female. Mean patient age at diagnosis was 13.3 years (range 1–17 years) with no statistical difference between both the groups (DC and UC – $p = .937$).

Prevalence of ID and IDA at diagnosis was 76.8% and 43.5%, respectively. After one year follow-up, ID decreased to 68.1% ($p = .182$) and IDA to 21.7% ($p = .002$). At diagnosis, 12 patients presented with severe anemia, after one year four patients still presented Hb levels under 100g/L (Table 1).

Mean hemoglobin levels were significantly higher after one-year follow-up (mean Hb levels at diagnosis: 117g/L and after one-year follow-up: 128g/L – $p = .0001$) and mean CRP values were significantly lower (at diagnosis 29.78mg/L and after one year 7.87mg/L – $p < .001$). There were no significant changes in mean ferritin levels (52.29ng/mL at diagnosis and 42.47ng/mL after one-year follow-up $p = .146$).

Table 1. Prevalence of anemia, severe anemia, iron deficiency and iron deficiency anemia at diagnosis and after one year follow-up.

	At diagnosis	After 1 year follow-up	*p* Value
Anemia	36/69 (43.5%)	17/69 (24.6%)	.0001
Anemia Hb <100g/L	12/69 (17.4%)	4/69 (5.8%)	.020
Iron Deficiency	53/69 (76.8%)	47/69 (68.1%)	.182
Iron Deficiency Anemia	30/69 (43.5%)	15/69 (21.7%)	.002

At diagnosis, mean Hb levels were significantly higher for CD patients ($p = .009$) but, after one-year follow-up, were similar for both pathologies ($p = .901$). After one-year follow-up, mean CRP values decreased below 10 mg/L for both groups but were higher for patients with CD ($p = .005$). CD patients presented superior ferritin values ($p = .0001$ and $p = .010$). IV iron was administered to 92.8% ($n = 64$) of patients. Ten patients started treatment with oral iron but interrupted it because of gastrointestinal intolerance. IV administration was equally preferred in both pathologies ($p < .001$ and $p < .001$).

During 15 years, 441 infusions of IV iron were conducted in that Unit, with a mean cumulative dose per patient of 832.95 mg and a mean dose per weight of 2.26mg/kg. During the entire follow-up period, each patient received a mean of eight treatments. Considering the total number of infusions occurred in that unit, about 50% were performed during patient's first year of follow-up. On average, each patient received from 2 to 10 infusions per treatment to prevent iron deficit or to restore total deficit. Overall cumulative dose during the first year was superior for UC patients (875mg vs 452.94mg – $p = .008$), however, during the entire study period, cumulative dose was similar for both UC and CD patients (989.47mg vs 762.14 – $p = .219$). No adverse reactions were reported. There were no clinical infections following IV iron treatment. Median time between diagnosis and first infusion of IV iron was higher for UC patients (2 (min 0; max 72) months vs 7 (min 0; max 65) months – $p = .277$). Analyzing all IV iron administrations, we found that severe disease was associated with lower Hb levels at diagnosis ($r = -0.139$ significant correlation for significance level .01) and higher cumulative iron sucrose doses over the course of the study ($r = .267$ significant correlation for significance level .05).

Crohn's disease

Changes in prevalence of ID, IDA and anemia in CD are summarized in Table 2.

During study period, 49 patients were diagnosed with CD, 46.9% feminine and 53.1% masculine; mean age 13.29 years (range 1–17 years). At the moment of diagnosis, disease activity was classified as 'moderate' in 79.6% of patients and as 'severe' in 16.4%, according to PCDAI and CRP values.

In CD patients mean hemoglobin concentration at diagnosis was 121g/L (85–165g/L) and after one-year follow-up, there was a significant increase to 129g/L (81–168g/L) – $p = .0001$. The proportion of patients with Hb <100g/L decreased from 10.2% to 4.08% ($p = .034$). There was a significant decrease in CRP values (from 27.46 to 9.93 mg/L – $p = .0001$), reflecting a good control of the disease after one-year follow-up. Ferritin showed no significant alteration after one year (65.16ng/mL at diagnosis and 49.15ng/mL after one-year follow-up – $p = .068$).

Mean cumulative dose of IV iron received during study period was 762.14mg (min 100mg; max 3300 mg); during the first year 60% of that dose was administered (452.94mg – min 100 mg; máx 2300 mg); mean dose of iron sucrose per weight received in one day was similar in both periods (2.31mg/kg vs 2.36mg/kg – min 1.23 mg/kg; max 11.36 mg/kg). On average, each CD patient needed two to four IV iron infusions per treatment. Mean time since diagnosis until the first IV iron administration was 2 months (min 0; max 72 months).

Ulcerative colitis

Changes in prevalence of ID, IDA and anemia in UC are summarized in Table 3. During the study period, 20 patients were diagnosed with UC, 60% feminine and 40% masculine; mean age 13.35 years (range 5–17 years). At the moment of diagnosis, disease activity was classified as 'moderate' in 50% of patients and as 'severe' in 35%, according to PUCAI values and clinical features.

In UC patients, mean hemoglobin concentration at diagnosis was 107g/L (50–146g/L) and after one-year follow-up there was a significant increase to 128g/L (82–156g/L) – $p = .009$. The proportion of patients with Hb <100g/L decreased from 30% to 10% ($p = .026$). There was a significant decrease in CRP values (from 35.45 to 2.82mg/L – $p = .005$) reflecting a good control of the disease after one-year follow-up. Ferritin showed no significant alteration after one year (20.75ng/mL at diagnosis and 26.1ng/mL after one-year follow-up – $p = .555$).

Mean cumulative dose of IV iron received during study period was 989.47mg (min 100mg; max 2800 mg); during the first year was administered 88% of total dosage (875mg – min 100 mg; max 1500 mg), mean dose of iron sucrose per weight received in one day was higher in the first year (2.9mg/kg vs 2.5mg/kg – min 1.25mg/kg; max 11.9mg/kg). On average, each UC patient received 2–10 infusions per treatment. Mean time since diagnosis until the first IV iron administration was 7 months (min 0; max 65 months).

Discussion

To our knowledge, there are few studies that report the prevalence of IDA and ID in the pediatric population with IBD. The results obtained are in accordance with previous

Table 2. Prevalence of anemia, severe anemia, iron deficiency and iron deficiency anemia at diagnose and after one year follow-up in Crohn's disease patients.

	At diagnose	After 1 year follow-up	*p* Value
Anemia	23/49 (46.9%)	11/49 (22.4%)	.0001
Anemia Hb <100g/L	6/49 (12.2%)	2/49 (4.01%)	.034
Iron Deficiency	34/49 (69.4%)	31/49 (63.3%)	.473
Iron Deficiency Anemia	17/49 (34.7%)	10/49 (20.4%)	.051

Table 3. Prevalence of anemia, severe anemia, iron deficiency and iron deficiency anemia at diagnose and after one year follow-up in Ulcerative Colitis patients.

	At diagnose	After 1 year follow-up	*p* Value
Anemia	13/20 (65%)	6/20 (30%)	.031
Anemia Hb <100g/L	6/20 (30%)	2/20 (10%)	.026
Iron Deficiency	19/20 (95%)	16/20 (80%)	.083
Iron Deficiency Anemia	13/20 (65%)	5/20 (25%)	.017

studies revealing that the prevalence of ID was higher than IDA's [1,2,20]. We concluded that iron sucrose treatment significantly decreased the prevalence of IDA after one-year follow-up. In fact, more than 50% of the iron cumulative dose was administered during the first year.

Globally we achieved a good disease control in our patients after one year, as the mean CRP values significantly decreased under 10mg/L for both pathologies. Therefore, we hypothesize that the non-significant decrease in ID and the persistence of anemia was a consequence of some patients requiring more iron to restore their reserves as well as other confounding factors such as anemia of chronic diseases.

In fact, one cannot forget that IBD pathophysiology itself gives patients a predisposition to an imbalance in iron's metabolism. Indeed, these patients not only tend to have a diet poor in many nutrients, including iron but also, present impaired absorption and increased intestinal blood loss, especially those with UC. All of these associated with increased requirements during growth explains a tendency to iron deficiency [2,8,11,21]. Also we believe that in some cases IDA/ID could be underdiagnosed.

UC group presented a higher prevalence of anemia and severe anemia. That can be explained because those patients tend to lose more blood when disease relapses [1,17]. Recently published ECCO guidelines [17] consider intravenous iron as the first line option in ID/IDA treatment and recommend that IV iron therapy should be initiated as soon as the serum ferritin levels started to drop. Our unit's protocol for the treatment of ID and IDA follows those guidelines and the authors consider that aggressive treatment and screening of ID/IDA has a major influency on disease control; we consider WHO definition of anemia and define ID and IDA according to disease activity index (PUCAI and PCDAI) and values of serum ferritin and CRP (serum ferritin $<30\mu g/L$ when CRP <10mg/L and serum ferritin $<100\,\mu g/L$ when CRP >10mg/L). We apply the same guidelines to UC and CD patients. Our results, despite having some limitations, support previous studies, proving that IV iron therapy is safe, feasible and effective using the lowest recommended safe dose ($\sim$3mg/kg, maximum 200 mg/infusion) [2,6,8,9,15].

We have not reported any side effects associated with IV iron therapy. On the other hand, patients who tried oral iron therapy had to interrupt it because of gastrointestinal intolerance, non-adherence or bad response. From our experience with IV iron therapy, we reinforce its safety profile, largely studied in the adult population, since no adverse effects were observed. Once more it is proven that IV iron therapy is able to bypass gastrointestinal intolerance of oral iron while allowing for higher single doses to be administered in shorter periods of time [2,9,15,17,22]. With this study, we hope to provide a significant impact on quality of life and disease control of patients by treating ID and IDA. Furthermore, as it was reported before by Danko et al. in 2016, for patients requiring periodic IV access it wasn't difficult to incorporate IV iron treatment in their routine, and we notice that it was better tolerated than adding another oral medication [6,15].

In our hospital we have only recently started to have access to FCM, so all of these administrations refer to iron sucrose. In our study, we reported mean cumulative doses of 832mg that sometimes required 5 administrations. While, Laass et al. [8], and later Azevedo et al. [9], reported mean cumulative doses of FCM of 821mg and 811.5mg, respectively, administered in 2 and 1 administrations. This is consistent with previous reports that indicate that iron sucrose requires more infusions and higher doses to replace total deficit.

There are few studies in pediatric patients using FCM. This formulation has the advantage to permit higher single doses of iron to be administered in shorter periods of time with less overall infusions improving the quality of life and resource saving [8]. Azevedo et al. in 2016 have proven that FCM is equally effective as iron sucrose and achieved higher mean Hb levels. [9] They reported mean Hb values of 131g/L in FCM-treated patients group compared to our mean Hb levels of 128g/L that were similar to those in their group treated with iron sucrose.

We recognize that the retrospective nature of this study may introduce bias. For example, the lack of a comparison with oral therapy and blood results six weeks after IV iron infusion inhibits the correct evaluation of iron therapy efficacy. In fact, with this study, we can only imply indirectly its efficacy by evaluating changes in Hb values and ID/IDA prevalence after one-year follow-up. Also, due to the observational nature of this study, we cannot confirm that the patient recovery from ID/IDA is only related to iron supplementation, other variables should be studied. We believe that we tend to select the most critical patients since those are more likely to have frequent blood analysis (besides the regular analytic control from 3 to 3 months), thus we might be underdiagnosing ID and IDA in milder patients.

Overall, despite further randomized controlled studies being needed on this matter, the authors recommend the use of IV iron as the first line in the treatment of IDA and ID in IBD pediatric patients. Reliable diagnostic criteria to timely identify ID and IDA are valuable since a prompt intervention has a significant impact on quality of life and disease control.

Disclosure statement

The authors report no conflicts of interest.

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