

ORIGINAL PAPERS

Efficacy of intravenous iron in treating iron deficiency anaemia in patients with inflammatory bowel disease. Are there predictors of response?

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ABSTRACT

Introduction: in inflammatory bowel disease (IBD) iron deficiency anaemia (IDA) is a very common disorder. Until recently, oral iron has been the mainstay therapy, nevertheless it has been associated with intolerance and noncompliance. Therefore, the goal of our study was to evaluate the efficacy of intravenous iron in IDA in IBD patients and the secondary aim was to investigate whether other potential factors could influence in the response to the treatment.

Design: an open-label, prospective, consecutive, single centre study.

Methods: we performed our study in patients with ulcerative colitis (UC) or Crohn's disease (CD) with severe anaemia or intolerance with oral iron. All of them received intravenous saccharose iron and did biochemistry profile with haemoglobin (Hb). Moreover, the correlation with other variables was studied: age, sex, smoking habit, IBD type, previous surgery and type of surgery and other treatments. Response was defined as Hb increase of ≥ 2 g/dL or normalization of the levels.

Results: fifty-four patients were included into the study, 34 (63%) with UC y 20 (37%) with CD, 18 (33.3%) men and 36 women (66.6%) and the average was 48 ± 14 years. The total proportion of responders was 52% (SD \pm 05); 43% of the patients reached Hb ≥ 2 g/dl and y 9% of them normalized Hb. Only the utilization of 5-ASA was associated with low response to iron treatment ($p < 0.05$).

Discussion: our study suggests that response to intravenous iron is achievable in the majority of patients with IBD and severe IDA or intolerance treatment with oral iron. Moreover, the patients with consumption of 5-ASA could had less response to the treatment.

Key words: Anaemia. Inflammatory bowel disease. Intravenous iron.

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INTRODUCTION

Compared with other complications, anaemia has traditionally been underestimated and it has received little attention from gastroenterologists (1-6). Because of this, it does not exist appropriate strategies for the adequate treatment of anaemia and nevertheless, anaemia is a relevant condition that may affect quality of life (7,8).

The causal conditions of anaemia include chronic disease, vitamin B12 deficiency, folate deficiency, medication-induced bone marrow suppression and macrocytic anaemia, haemolysis, and most frequently, iron deficiency anaemia (IDA). IDA predominantly results from chronic blood loss in the intestine, but also iron malabsorption, resection or impaired dietary intake, may contribute to its development (1,4-6,9-11).

The therapy with oral iron is very common in patients with inflammatory bowel disease (IBD), but this therapy has been associated with intolerance and discontinuation due to side effects are frequent (6,9). In contrast, parenteral iron administration prevents many of the issues associated with oral ingestion, such as bowel malabsorption and intolerance, and, at the same time, the introduction of more stable and effective transporters, including iron sucrose, allows complete storage reposition with few infusions (1,12,13). In spite of this, the response to the supplementation with intravenous (i.v.) iron is changeable in this type of patients, without knowing predictors of response.

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Therefore, the primary end-point of the present study was to evaluate the efficacy of i.v. iron treatment in iron deficiency anaemia (IDA) with IBD patients and the secondary aim was to investigate whether other potential factors could influence in the response to the treatment.

METHODS

Design

This was an open label, descriptive, in one single centre and with included consecutive cases.

Patients

Patients who were visited at the IBD consult with confirmed diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) according to established criteria of Montreal Classification (14) who had severe iron deficiency anaemia or intolerance treatment with oral iron were selected and included during a period of twelve months. All of them were patients older than 18 years old and severe IDA (haemoglobin < 10 g/dl) or intolerance treatment with oral iron.

Anaemia was defined as haemoglobin (Hb) levels above 12 g/dL in females and 13 g/dL in males according to the World Health Organization (WHO) (15). In addition, the patients had to have a biochemistry profile suggestive of iron deficiency, defined by at least one of the following analytical criteria: low serum iron (< 59 µg/dL); low ferritin (< 30 µg/L); low transferrin saturation (< 12%); or high transferrin concentration (> 400 mg/dL). The mean Hb level from two screening visits was used to justify inclusion.

Patients were excluded from the study if they had had treatment or if untreated vitamin B12 or folate deficiency, other types of anaemia, erythropoietin treatment within 8 week prior to enrolment or blood transfusion within 30 days.

Response was defined as Hb increase of ≥ 2 g/dL or Hb ≥ 12 g/dL in women and Hb ≥ 13 g/dL in men.

Iron treatment

We used 200 mg i.v. of iron twice a week up to the total amount estimated bases on the formula:

Iron deficiency (mg) = [Weight (kg) x (Target Hb – Current Hb (g/dL))] + 500 (estimated storage deficiency for iron reposition) (16).

In our study we used i.v. iron sucrose (Venofer, Grupo Uriach) in i.v. infusion, 2 ampoules (200 mg of iron sucrose) were diluted in 200 ml sterile 0.9% m/V sodium chloride solution. In the first infusion, iron should be infused at a rate of 60 ml in 60 minutes and the rest of the

dose at 125 ml/h. Moreover, vital signs were measured each half and hour.

Clinical and laboratory parameters were monitored one week before and one week after the last dose of iron. The haematological controls included, at least, Hb, haematocrit and iron-related parameters (concentrations of iron, ferritin and transferrin). It was evaluated as possible factors predictors of response demographic (age, sex and smoking habit) and clinical variables (IBD type, surgery type and extraintestinal manifestations) as soon as other treatments (5-ASA, prednisolone, azathioprine, infliximab, adalimumab, anticoagulants and antiaggregants).

Statistical analysis

The variables were expressed as mean, standard deviation (SD), percentages and odd ratio (and 95% confidence intervals [CI]). A level of $p < 0.05$ was considered statistically significant. Stepwise multivariate analysis was performed to study the correlation between basal haemoglobin and haematocrit concentrations and other variables: age, sex, smoking habit, IBD type, anemia type, surgery type, extraintestinal manifestations and other treatments (5-ASA, prednisolone, azathioprine, infliximab, adalimumab, anticoagulants and antiaggregants). All analyses were conducted using the computer-based statistics software program SPSS.

RESULTS

From the 623 patients who were enrolled into the study, 54 patients were included. Mean patient age was 48 ± 14 (SD), 31% of whom were male and 24% smokers. Of these, 34 were ulcerative colitis and 20 Crohn's disease, with severe anaemia 54.6%, with intolerance to the oral iron 31.8% and with absence of response 13.6%. The demographic, clinical and therapeutic characteristics are showed in table I.

The total proportion of response was 52% (SD ± 0.5), Hb ≥ 2 g/dL was reported in 43% and 9% of patients reached normal levels of Hb; without differences of response between both types of IBD. The average increase in haemoglobin was 1.9 ± 1.7 g/dL, from 9.9 ± 1.8 g/dL to 11.9 ± 1.9 g/dL ($p < 0.001$) and the average increase in haematocrit was 5.3 ± 4.4 , from 31.6 ± 4.4 to 36.9 ± 4.4 % ($p < 0.0001$). The difference between the mean Hb and haematocrit at baseline and after treatment was statistically significant ($p < 0.0001$). Only 3 patients showed a decrease of the levels of haemoglobin and haematocrit.

The tolerance of i.v. iron was 100%, therefore the treatment did not present discontinuation.

There is no difference between the response to the iron and the type of anaemia, it is to say, the response did not depend on the initial Hb. In the multivariate analysis,

only the utilization of 5-ASA was associated with response to iron treatment (OR 0.11; IC 95%: 0.01-0.86). No association was found with age, sex, smoking habit, type of anaemia, surgery and type of surgery, extraintestinal manifestations, type of IBD or other extraintestinal manifestations.

DISCUSSION

The results of this study suggest that i.v. iron could be effective as well as good tolerated in patients with IBD with severe anaemia or intolerance treatment with oral iron.

A common misconception is to believe that anaemia is an infrequent process in IBD patients (3). The reported prevalence of anaemia in these type of patients varies between 9 to 74% and the studies included the anaemia as the most common systemic complication of IBD (2,17).

In the articles published concerning the aetiology of anaemia the most important causal condition is iron deficiency, as consequence of chronic blood loss in the intestine (predominantly in developed countries) (4-6) but also because of dietary restrictions, malabsorption and/or resection (in Crohn's disease) (18). The prevalence ranged from 36-90% depending on the cohort and even more on the definition of iron deficiency. Besides Wilson study reports that 10 to 73% outpatients and 30 to 70% of inpatients with Crohn's disease present anaemia (14). In our case, one outpatient study, severe anaemia or intolerance treatment with oral iron is present in 6.8% of the patients, therefore, the anaemia is not an incidental finding and our goal has to be reach normal levels of Hb and improve the patient's quality of life (6,7).

In clinical practice, oral iron supplementation is a common part of the management of anaemia (22). In contrast, despite clinical comparative trials show faster and prolonged response with i.v. iron (12), parenteral iron (23,24) is only recommended when there is intolerance to oral preparation or noncompliance and there is unknown knowledge about the efficacy of this type of treatment in IBD, although in the general population has been demonstrated in numerous studies (13). With this background in mind, this study was conducted to clear the efficacy of i.v. iron sucrose for the treatment of IDA with IBD patients. Our data demonstrate that iron parenteral could be an excellent therapy in the manage of IDA in IBD. In this way, it has been observed that all 3 of the 54 patients experienced a decrease of the concentration of Hb and haematocrit concentrations an only 52% of the patients normalized or increased Hb ≥ 2 g/dL. These results do not demonstrate accordance with published data previously in the literature (12,25-28), so the high efficacy of the treatment could not be confirmed in our study, although if we think about the correlation between increase of Hb and quality of life, the supplementation keep on constituting very recommended. May be, it would be necessary

Table I. Demographic, clinical and therapeutic characteristic

<i>General characteristics</i>	
Age, years	48 \pm 14
Male, %	33.3
Smoking habit, %	24.1
Anaemia, n	54
Severe anaemia, %	54.6
Intolerant, %	31.8
No response, %	13.6
Crohn's disease, n	20
A1 (< 17 years), %	5.0
A2 (17- 40 years), %	80.0
A3 (> 40 years), %	15.0
B1 (non-structuring, non-penetrating), %	40.0
B2 (structuring) %	10.0
B3 (penetrating) %	50.0
L1 (terminal ileum), %	55.0
L2 (colon), %	15.0
L3 (ileocolon), %	30.0
L4 (the upper gastrointestinal location), %	0.0
Surgery, n	13
Ileum resection, %	5.6
Intestinal resection, %	5.6
Perianal abscess, %	3.7
Colon resection, %	1.9
Fistula & flanges, %	1.9
Abscess & fistula, %	3.7
Total colectomy, %	1.9
Drugs, n	54
Prednisolone, %	38.9
5-ASA, %	61.1
Azathioprine, %	27.8
Infliximab, %	1.9
Infliximab & azathioprine, %	25.9
Adalimumab, %	1.9
Antiaggregants & anticoagulants, %	1.9

more studies of cost-effectiveness for drawing strong conclusions.

On the contrary of Mamula's study, where there were adverse events in 9% of the patients, our study demonstrated safety and tolerability in 100% of the patients, everybody finished the treatment without interruption.

Apart from the efficacy, we tried to investigate whether the response to the treatment depended on the other variables. Our study suggests that these changes in Hb could be associated with the consumption of 5-ASA, it would mean that people, who take 5-ASA, had less response to the treatment that people with other different treatment. Sulfasalazine can reduce folic acid absorption by inhibiting the enzyme jejunal folate conjugase competitively, so this mechanism can contribute to anaemia, but it does not happen in our study because patients with folate deficiency were excluded. Rectal bleeding is a frequent symptom in ulcerative colitis and patients with proctitis can loose

red blood or even blood with clots. By the way, if 5-ASA is treatment for maintenance in mild or moderate ulcerative colitis, we could think that 5-ASA can be related with IDA, and therefore ulcerative colitis could be a confusion factor, but nevertheless, in inclusion analysis, the ulcerative colitis do not change the odds ratio.

There are few studies about predictors of response in patients with anaemia and IBD and in most of them, only iron-related parameters are analyzed just as it happens in Gasche (25) multicentric study, which suggests relation between response to i.v. iron and EPO, sTfR and transferrin. The same as our date, the sample size is small in order to give recommendations; nevertheless, it is very important to identify possible factors which can change the response to the treatment.

In our study, there are some limitations. We only include outpatients; therefore we can underestimate global data of anaemia because we do not include severe forms. Moreover, it would be recommended to do a new blood analysis one month after the last dose of iron because the percentage of response probable could be better.

In summary, the conclusions of our study suggest that response to i.v. iron is achievable in most of the patients with IBD and severe IDA or intolerance treatment with oral iron. Moreover, the use of sulfasalazine could decrease the response to the iron.

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