Improvement of Anxiety, Depression and fatigue after treatment of Anemia in patients with inflammatory bowel disease patients

Melhora da Ansiedade, Depressão e fadiga após tratamento de Anemia em pacientes com doença inflamatória intestinal

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Tatiane de Alvarenga Antunes
Graduanda em Medicina
Institution: Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (SUPREMA)
Address: Rua Frederico Lage, 71, Mariano Procópio, Juiz de Fora – MG, CEP 36080-110
E-mail: tatiliantunes@gmail.com

Priscila de Alvarenga Antunes
Médica do setor de Emergência
Institution: Hospital Medsênior – Vitória
Address: Avenida Dante Michelini, 2431 - 401, Palazzo Venezia, Vitória – ES,
CEP: 29066-430
E-mail: prikantunes@gmail.com

Bruno Kappel Nascimento
Graduando em Medicina
Institution: Centro Universitário de Valença (UNIFAA)
Address: Frederico Lage, 75, Mariano Procópio, Juiz de Fora - MG CEP: 36080-110
E-mail: brunoknascimento@gmail.com

Angelo Tabet Zanini
Graduando em Medicina
Institution: Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (SUPREMA)
Address: Rua Maceió, 415, casa 101, Parque Jardim da Serra, Juiz de Fora – MG,
CEP: 36038-610
E-mail: angelo.tabet.zanini@gmail.com

Jossiely Rodrigues Pinheiro
Graduanda em Medicina
Institution: Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (SUPREMA)
Address: Rua Olegário Maciel, 476 - 490, Juiz de Fora – MG, CEP: 36015-350
E-mail: jossypinheiro@hotmail.com

Maria Cláudia Ferreira Bezerra de Azevedo
Graduanda em Medicina
Institution: Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (SUPREMA)
Address: Avenida Presidente Itamar Franco, 2552 - 1303, Juiz de Fora – MG,
CEP 36025-290
E-mail: mfamedicina@gmail.com

Cristiano Rodrigo de Alvarenga Nascimento
Pós-Doutorado pela Universidade Nove de Julho (UNINOVE – SP)
Institution: Department of Research, Development and Innovation, Innovative Health System Health Management (IHS Medicine and Technology)
Address: Avenida Alceu Wamozy, 272, Vila Mariana - São Paulo, CEP: 04105-040
E-mail: cnascimento@ihsmed.com.br

Carla Valéria de Alvarenga Antunes
Doutorado pela Universidade Federal de Juiz de Fora (UFJF)
Institution: Department of Research, Development and Innovation, Innovative Health System Health Management (IHS Medicine and Technology)
Address: Avenida Alceu Wamozy, 272, Vila Mariana - São Paulo, CEP: 04105-040
E-mail: carlavaleria.aantunes@gmail.com

ABSTRACT
INTRODUCTION: Anemia is a common complication in inflammatory disease bowel (IBD). Many patients have this comorbidity ignored during clinical follow-up. Nonetheless, studies of anemic patients have a significant relationship between anemia and higher anxiety, depression and fatigue. This study evaluated the level of anxiety, depression and fatigue before and after treatment for anemia in mild anemic, IBD patients from the IBD Center of the UFJF University Hospital. OBJECTIVE: The objective of the present study was to investigate the improvement of anxiety, depression and fatigue after treatment of anemia in IBD patients. METHODS: In this cross-sectional study, 100 patients with CD (Crohn's disease) and 100 with RCUI (ulcerative colitis) were screened for anemia. For evaluation of anemia, complete blood count, ferritin, saturation index transferrin, serum levels of folic acid, serum iron and vitamin B12 was performed. In anemic patients, was evaluated and compared the levels of anxiety, depression and fatigue before and after anemia treatment. For the evaluation of anxiety was applied the hospital anxiety and depression scale (HADS), to assess fatigue was applied Chalder`s questionnaire. RESULTS: The evaluation average for anxiety before anemia treatment was 7.3 ± 4.3 and after treatment it was 5.3 ± 4.8 (p=0.0.08), the average of depression before treatment was 6.2 ± 5.2 and after treatment it was 4.9 ± 4.8 (p=0.08) and the average of fatigue before anemia treatment was 30.9 ± 8.7 and after treatment it was 21.6 ± 8.4 (p<0.001). Treatment with oral liposomal iron was effective in improving mild IDA and quality of life, as well as in decreasing fatigue in patients with inactive or mildly active IBD. CONCLUSION: The treatment of anemia in patients with IBD Brazilian outpatients showed statistically significant improvement in cases of anxiety and fatigue, although did not demonstrate a significant improvement in depression.

Keywords: inflammatory bowel disease, Anemia, ulcerative colitis, Crohn’s disease, quality of life, fatigue, Anxiety, Depression.

RESUMO
INTRODUÇÃO: A anemia é uma complicação comum em doenças inflamatórias intestinais (DII). Muitos pacientes têm esta comorbidade ignorada durante o acompanhamento clínico. No entanto, estudos de pacientes anêmicos têm uma relação significativa entre anemia e maior ansiedade, depressão e fadiga. Este estudo avaliou o nível de ansiedade, depressão e fadiga antes e depois do tratamento de anemia em pacientes com anemia leve, IBD do Centro IBD do Hospital Universitário da UFJF. OBJETIVO: O objetivo do presente estudo foi investigar a melhora da ansiedade, depressão e fadiga após o tratamento da anemia em pacientes com DII. MÉTODOS: Neste estudo transversal, 100 pacientes com DC (doença de Crohn) e 100 com

RCUI (colite ulcerativa) foram submetidos a uma triagem para detecção de anemia. Para avaliação da anemia, foi realizado um hemograma completo, ferritina, índice de saturação transferrina, níveis séricos de ácido fólico, ferro sérico e vitamina B12. Em pacientes anêmicos, foram avaliados e comparados os níveis de ansiedade, depressão e fadiga antes e depois do tratamento da anemia. Para a avaliação da ansiedade foi aplicada a escala de ansiedade e depressão hospitalar (HADS), para avaliar a fadiga foi aplicado o questionário de Chalder. RESULTADOS: A média da avaliação da ansiedade antes do tratamento da anemia foi 7,3 ± 4,3 e após o tratamento foi 5,3 ± 4,8 (p=0,0,08), a média da depressão antes do tratamento foi 6,2 ± 5,2 e após o tratamento foi 4,9 ± 4,8 (p=0,08) e a média da fadiga antes do tratamento da anemia foi 30,9 ± 8,7 e após o tratamento foi 21,6 ± 8,4 (p<0,001). O tratamento com ferro lipossômico oral foi eficaz para melhorar a IDA leve e a qualidade de vida, assim como para diminuir a fadiga em pacientes com IBD inativa ou levemente ativa. CONCLUSÃO: O tratamento da anemia em pacientes com IBD em pacientes ambulatoriais brasileiros apresentou melhora estatisticamente significativa nos casos de ansiedade e fadiga, embora não tenha demonstrado uma melhora significativa na depressão.

Palavras-chave: doença inflamatória intestinal, Anemia, colite ulcerativa, doença de Crohn, qualidade de vida, fadiga, Ansiedade, Depressão.

1 INTRODUCTION

Inflammatory bowel diseases (IBD) are multisystem conditions that entail substantial personal cost for many patients due to the unpredictable fluctuating course of symptoms, absenteeism at work, and to continuous need of expensive drugs, surgeries, and multidisciplinary care [1].

Iron deficiency anemia (IDA) is one of the most common IBD complications [2]. The IDA mechanism in IBD is multifactorial and includes increased blood loss due to gastrointestinal inflammation, as well as decreased iron absorption, loss of appetite, and block of intestinal iron uptake [3]. Importantly, anemia can contribute to patients' poor quality of life [4]. In addition, anemia is a significant predictor of increased hospitalization risk, as well as of increased mortality in IBD patients [5].

Mental disorders represent a serious public health problem as they significantly compromise the quality of life of an individual, being among the greatest causes of disability in the world. Anxiety and depression disorders are highly prevalent and affect the mood and feelings of those affected, changing the way they see the world and reality as well as influencing emotions, mood, and lifestyle in general [6].

According to a systematic review, it is estimated that the mean prevalence of anemia in IBD is approximately 20% in outpatients and 68% in hospitalized patients [7]. It is well known that the correction of anemia has beneficial impact on patients' quality of life. Therefore, screening, diagnosing and managing anemia in IBD should be part of the efforts to improve the

quality of the care provided to all IBD patients.

Oral ferrous iron formulations such as ferrous sulfate, ferrous gluconate and ferrous fumarate have been traditionally used to treat mild IDA in several conditions, including IBD [7,8]. Unfortunately, although the oral iron treatment is cheaper and convenient, it is not always well tolerated due to gastrointestinal side effects [9,10]. Moreover, a huge proportion of the oral ferrous iron salts administered to patients is not absorbed and subsequently undergoes oxidation in the gut lumen and/or mucosa, fact that leads to the generation of reactive oxygen species able to damage the intestinal epithelium [11-14]. However, clinical studies have found that patients treated with oral iron showed no significant increase in IBD activity [15,16]. Nonetheless, it is worth emphasizing that even when the therapy with oral traditional iron formulations is well tolerated, part of the IBD patients does not respond to it and requires intravenous iron treatment [15,16].

The liposomal iron, a preparation of ferric pyrophosphate carried within a phospholipid and sucrose esters of fatty acid membrane, is a new generation of oral iron, which shows high gastrointestinal absorption and high bioavailability [17,18]. In comparison with others oral traditional iron preparations, the liposomal iron seems to be a promising new iron replacement strategy in IDA patients, since it presents low incidence of side effects [19]. So, this is the formulation that we chose for treating the patients.

To the best of our knowledge, there is no published peer review study concerning the treatment of IDA in improving fatigue, anxiety and quality of life in patients with inactive or mildly active IBD patients. It is worth determining whether the oral liposomal iron is able to mitigate anemia without triggering an IBD flare and improving patient's quality of life. Therefore, this pilot study was designed to assess the impact of this treatment on psychometric scores in inactive ou mildly active IBD patients.

2 METHODS

This is open-label pilot study conducted from November 2017 to June 2018, in adult outpatients with IBD attended in Inflammatory Bowel Disease Center at the University Hospital of Federal University of Juiz de Fora, Brazil. The IBD diagnosis was based on clinical, radiological, endoscopic and histopathological criteria generally accepted for ulcerative colitis (UC) or Crohn disease (CD) [20].

The study protocol was defined in accordance with the Declaration of Helsinki and approved by our Institutional Ethics Committee. All patients signed a free and informed consent form before being included in the study. They could withdraw their consent or discontinue their

participation at any time. This trial was registered on NCT02760940 in 07-08th-2016.

3 PARTICIPANTS

Patients with IBD were eligible if they were age ≥ 18 years and ≤ 65 years with inactive or mildly active disease and had a diagnosis of mild anemia. Mild anemia was defined as hemoglobin between 11.0-11.9 g/dL in women and 11.0–12.9g/L in men [21,22]. Iron deficiency was defined by serum ferritin < 30 µg/L in patients without clinical or biochemical evidence of active IBD; in the presence of inflammation, a serum ferritin ≤ 100 µg/L was consistent with iron deficiency [22].

Patients were not included in the study whenever any of the following conditions were found in the initial screening: patients younger than 18 or older than 65 years, moderately-to-severely active IBD, pre-existing chronic disease (e.g. liver disease, kidney failure, clinically significant pulmonary or heart diseases), systemic infection in the previous 3 months, current history of any type of malignancy (except for skin cancer), alcohol abuse (daily alcohol consumption above 20 g), drug addiction, previous gastrectomy, history of total colectomy or extensive intestinal resection (> 100 cm), hemoglobin < 11.0 g/dL, folate, or vitamin B12 deficiency, or replacement therapy using iron, folic acid or vitamin B12 in the previous six months. Pregnant women or nursing mothers were also excluded.

4 MEASUREMENTS AND OUTCOMES

4.1 BASELINE CHARACTERISTICS

At entry, the eligibility criteria were assessed, and patients' medical history recorded. The following patient's relevant data were gathered in the initial assessment: age, gender, smoking status. Disease-associated variables evaluated were type of IBD, location, and phenotype (for CD), according to the Montreal classification [23]. CD activity was measured through the Harvey-Bradshaw Index (HBI). The HBI below 5 was considered as clinical remission, and scores between 5 and 7 were considered as mildly active disease (24,25). The disease activity for UC patients was determined according to the Truelove and Witt's criteria [26]. Thus, clinical remission was defined as ≤ 2 or 3 stools/day with no blood and/or pus, and no systemic symptoms; mild activity was defined as up to 4 stools/day, with or without blood, no systemic manifestation [26]. Biological activity was defined by C-reactive protein (CRP) level above 5 mg/L.

4.2 DISEASE-SPECIFIC QUALITY OF LIFE

The disease-specific quality of life (QOL) was assessed at baseline and at the 8th week using country-specific, validated version of the Inflammatory Bowel Disease Questionnaire (IBDQ). The cut-off points used in the IBDQ interpretation are based on previous study [24]: ≥ 200 (excellent), between 151 and 199 (good), between 101 and 150 (regular), and ≤ 100 (poor) [27].

4.3 FATIGUE MEASUREMENT

The participants were instructed to answer the fatigue questionnaire (Chalder Fatigue Scale) at the time they were included in the study and 8 weeks after the beginning of the treatment. The Chalder Fatigue Scale is a British instrument used to measure physical and mental fatigue and it has already been translated into Portuguese and validated in Brazil [28].

The questionnaire comprises 12 items related to the intensity of fatigue symptoms. The items were in bimodal scores. Items are rated on a 4-point Likert scale (0 = better than usual, 1 = no more than usual, 2 = worse than usual, 3 = much worse than usual), with higher scores indicating greater fatigue perception [28].

4.4 BIOCHEMICAL ASSESSMENT

The participants were instructed to fast 8 hours before the blood collection for follow-up routine analysis. Blood sample was collected from these patients in order to determine the following laboratory data: erythrogram, serum iron, ferritin, transferrin saturation (TfS), erythrocyte sedimentation rate (ESR) and quantitative CRP. Vitamin B12, and folate levels were measured to exclude patients with anemia caused by them.

5 INTERVENTION

After screening, the enrolled patients were supplemented with oral liposomal iron (Fisiogen Ferrol®, Zambon) for 8 weeks. The replenishment was provided to the patients on a *compassionate* use basis at the dose of two liposomal iron tablets per day (equivalent to 28 mg of liposomal iron). The patients were instructed to take the tablets at any time of the day, regardless of meals. They were monitored by telephone at weekly interval periods throughout the intervention phase in order to optimize their therapy adherence and check the occurrence of side effects. Furthermore, the Truelove and Witt's criteria, as well as the HBI, were monitored to evaluate occasional IBD flares in UC and CD patients, respectively, during the follow-up (at the 4th and 8th treatment weeks).

After the first 4 treatment weeks, the patients returned and brought the remaining oral iron tablets in order to allow assessing their adherence to the treatment and to receive a new set of drugs to complete the 8 treatment weeks. High adherence to the therapy was defined as the proportion of patients taking at least 80% of their prescribed medication, while low adherence as less than 80% of prescribed doses taken [29].

6 REASSESSMENT

The same instruments and hematological assessments performed at the entry were repeated at the end of the 8th treatment week with oral iron supplementation.

7 OUTCOME MEASUREMENTS

One essential endpoint of the study was the response rate to liposomal oral iron therapy in treating mild anemia in inactive or mildly active IBD patients. Treatment responders were defined as patients who achieved Hb increase of at least ≥ 1 g/dL and/or Hb normalization by the 8th treatment week. Hb normalization was defined as Hb values ≥ 12 g/dL for women or ≥ 13 g/dL for men [21].

The next endpoints included changes in ferritin concentration and TfS percentage from the baseline to the 8th week; impacts of the oral iron treatment on quality of life, and fatigue; changes in disease activity (assessed by HBI, Truelove and Witt's criteria, and CRP); adherence to therapy and treatment safety and tolerability.

8 SAFETY AND TOLERABILITY

Safety and tolerability were assessed based on adverse events (AEs) observed throughout the study and on routine hematological and blood chemistry indices. Patients who developed Hb concentrations 9.0 g/dL and/or disease flare during the study were withdrawn from the study to receive standard medical treatment. Serum pregnancy tests were conducted in female patients and the use of concomitant medications was assessed in all patients at each clinical visit. Other safety-related conditions for early discontinuation included pregnancy and serious adverse events (SAEs) related to the herein studied medication (based on investigator's opinion that there was a reasonable possibility that the event may be caused by the studied drug).

9 RESULTS

9.1 STUDY POPULATION

A total of 200 patients with inactive or mildly active IBD (100 with UC and 100 with CD) underwent screening and anemia was detected in 40 (20%) patients. Among them, 11 were not eligible to participate in the process due to lack of interest, pregnancy, surgical intercurrence or underlying cardiac insufficiency. Eight (23%) patients were not enrolled because they presented evidence of moderately active CD or severe anemia.

So, 21 patients (14 females) were included, 15 patients (71.4%) with CD and 6 (28.6%) with UC. Baseline demographic and clinical characteristics are depicted in Table 1. The mean age was 41.3 ± 14.6 years (range 18 - 62 years). About 25% presented previous intestinal resection, but none had short-bowel syndrome.

One UC patient presented proctitis, 3 left-sided UC and 2 extensive UC. Ileocolon was the most frequent location of CD (40%) followed by colon (33.3%). For CD disease, 4 patients had non-stricturing non-penetrating disease (26.7%), 9 had stricturing CD (60%) while the remained 2 patients had penetrating CD (13.3%). All recruited patients were on treatment for IBD: 15 (71.4%) were on azathioprine, 3 (14.3%) were on glucocorticoides, 5 (23.8%) patients were on anti-TNF agents while 3 (14.3%) were on salicylates.

The mean Hb level was 11.4 g/dl at baseline, while the mean serum iron and ferritin were 59.1 mg/dl and 98.8 µg/L, respectively.

9.2 TREATMENT RESPONSE

Thirteen of 21 patients (61.9%) responded to oral liposomal iron replacement therapy (mean increases of Hb 11.4 to 12.6 g/dL). Of these, 9 (69.2%) achieved Hb increase of at least ≥1 g/dL and 12 (92.3%) presented Hb normalization by the 8th treatment week. In addition, there were a significant improvement in baseline serum iron (59.1 to 86.8 mg/L; P = 0.005) and TfS (20.1% to 30.4%; P = 0.006) values after treatment with oral liposomal iron, despite no significant difference in ferritin values (Table 2).

9.3 DISEASE-SPECIFIC QUALITY OF LIFE, FATIGUE, AND DISEASE ACTIVITY

There was significant improvement in the IBDQ scores after the oral liposomal iron therapy for 8 weeks. The baseline IBDQ score for the cohort was 157 (±37) with a mean increase in the score by 26.4 (P <0.001) at week 8 compared to the baseline. In addition, we found a notable reduction in the perception of fatigue after 8 weeks of oral liposomal iron therapy compared to the baseline (30.9 vs. 21.6; p<0.001; Table 2). There was a linear correlation

between the increase in Hb levels and the improvement of QOL as evaluated by IBDQ (r = 0.54; P= 0.01; Figure 1).

Following oral liposomal iron therapy, no change was seen in clinical disease activity (P=0.10). In addition, C-reactive protein levels remains unchanged after treatment (P=0.98).

9.4 ADHERENCE TO THERAPY, SAFETY, AND TOLERABILITY

The adherence rate for oral liposomal iron was 81%. When looking at compliance to treatment, only four patients took less than 80% of the prescribed capsules (missing more than eight capsules) at the end of treatment. No adverse drug reactions or drug- attributed serious adverse events occurred. No patient was withdrawn from the study or was lost to follow-up.

10 DISCUSSION

This pilot study showed that oral liposomal iron replacement therapy in inactive or mildly active IBD patients with mild IDA was efficient and well tolerated showing a reduction in the perception of fatigue and an increment disease specific QOL in the studied population which correlated with the enhancement of serum hemoglobin levels.

IDA affects 13%-90% of IBD patients according to a recent series [30,31]. Oral iron traditional formulations in IBD patients may be troublesome and results in gastrointestinal side effects. Therefore, oral iron supplementation in IBD patients with IDA is challenging, and guidelines are prone to recommend the use of intravenous iron formulations [6]. On the other hand, those formulae are more expensive than oral iron and still bear the need for venous access and the infusion monitoring due to possible hypersensitivity reactions [9,16].

Nevertheless, initial clinical data in IBD patients suggest that oral iron formulations with improved tolerability, such as liposomal iron or ferric maltol, may represent a viable alternative to intravenous iron, at least for patients with mild-to- moderate IDA [32,33]. The administration of oral liposomal iron appears as a valuable option to treat mild IDA, and even more so for individuals with IBD who often present intolerance, worsen of gastrointestinal symptoms and lack of efficacy with other traditional oral iron salts formulations [19,34].

The present study used liposomal iron replacement therapy for eight weeks and observed a significant increase in Hb levels (mean increase: 11.4 to 12.6 g/dl), in IBD patients with correction of IDA in 62% of the total population and a statistically significant improvement significant in cases of anxiety and fatigue, although not demonstrated a significant improvement in the depression.

We found a good tolerability and high adherence to therapy, which can clearly be seen,

once all of the 21 (100%) completed the study, with 81% taking all the prescribed regimen. Four patients, who took less than 80% of the prescribed therapy, report forgetfulness as the reason for missing therapy. This finding is in accordance of those of Pisani and colleagues [19] that also observed good tolerability of liposomal iron in chronic kidney disease patients, with only minor side effects as constipation and diarrhea reported.

As already reported by several authors, the presence of anemia correlates directly with both a worsening in patients' QOL and the perception of fatigue [38-41]. This study showed an improvement in the QOL following iron therapy in patients with IDA, which was linearly associated with increment in Hb levels. Importantly, a significant reduction in fatigue perception was noted. Fatigue is an important clinical problem in patients with IBD and may contribute for lower health-related QOL in this population [40-41]. Thus, oral liposomal iron therapy in patients with IBD presenting concomitant mild IDA and fatigue may be useful for mitigating complain of fatigue in this setting.

The present study has some limitations. Firstly, it is a single-center pilot study with a small number of patients. Secondly, the iron preparation tested in the study contains a relatively low dose of elemental iron (28 mg) compared to traditional compounds, what can be a reason why the increase in Hb levels in our study were not so prominent. We can speculate that an increase in liposomal iron dosage could result in further increase in serum Hb levels and maybe better results in quality of life. Finally, the short-term course of treatment could have impacted the response, mainly regarding the scores of depression.

In summary, this pilot study provides actual data supporting the treatment of anemia with oral liposomal iron for decreasing anxiety and fatigue in mild anemic IBD patients with inactive or mild active IBD and paves the way for future studies evolving larger IBD populations utilizing higher doses of this drug and longer follow-up.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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ANEXOS

Table 1- Baseline demographic and clinical characteristics of patients

Characteristic	N (%)
Gender, (M:F)	7 (33.3): 14 (66.7)
Age, (yr) †	41.3 ± 14.6
Current smoker	1 (4.3)
Type of IBD, (CD:UC)	15 (71.4): 6 (28.6)
Disease location	
CD - [L1/L2/L3]	4(26.7) / 5 (33.3) / 6 (40)
UC - [E1/E2/E3]	1 (16.7) / 3 (50) / 2(33.3)
Disease behavior (CD), [B1/B2/B3]	4 (26.7) / 9 (60) / 2 (13.3)
Disease duration, (yr) †	6.2 ± 2.3
Previous intestinal resection	4 (19)
IBD-specific treatment	
Glucocorticoides	3 (14.3)
Anti TNFα agents	5 (23.8)
Aminodalicylates	3 (14.3)
Azathioprine	15 (71.4)

†- Mean ± standard deviation. UC = ulcerative colitis; CD = Crohn`s Disease; L1 = ileal; L2 = colonic; L3 = ileocolonic; E1 = ulcerative proctitis; E2 = left-sided UC; E3 = extensive UC (pancolitis); B1 = non-stricturing, non-penetrating; B2 = stricturing; B3 = penetrating.

Table 2: Outcomes after 8 weeks of treatment with oral liposomal iron

Variable	Baseline†	Week 8†	P value
Hemoglobin [g/dL]	11.4 ± 0.7	12.6 ± 1.3	0.003
Ferritin [µg/L]	98.8 ± 110.6	123.1 ± 126.7	0.25
Serum Iron [mg/L]	59.1 ± 23.8	86.8 ± 34.4	0.005
TfS [%]	20.1 ± 10.1	30.4 ± 15.1	0.006
C-Reactive Protein [mg/L]	7.1 ± 6.7	7.1 ± 9.6	0.98
HBI score	2.7 ± 1.9	2 1 ± 1.5	0.55
Fatigue score	30.9 ± 8.7	21.6 ± 8.4	< 0.001
IBDQ score	157 ± 37	183.4 ± 37.8	< 0.001

†- Mean ± standard deviation; TfS = *transferrin saturation;* HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire

Figure 1. Relationship between hemoglobin levels after treatment with oral liposomal iron and improvement in the perception of quality of life.