New Options in Management of Iron-Deficiency Syndromes in Inflammatory Bowel Diseases

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Abstract

The article describes the most common iron deficiency syndromes (IDS) in inflammatory bowel disease (IBD) and presents the modern principles of differential diagnosis of gastrointestinal disease, the advantages and disadvantages of standard methods for the correction of iron-deficiency (ID) and anemia in this group of patients.

The authors give a circumstantial outline of their own data regarding the examination and treatment of 77 patients with IBD and anemia and prove the necessity of compulsory serum ferritin (SF) testing as the most important differential marker of the IDs. Inadequate production of erythropoietin as the main cause of anemia was observed in 15% of patients with high SF values. On the contrary, the necessity of mandatory use of iron preparations in management of anemia was determined in 85% of patients. The high effectiveness and safety of Sucrosomial® iron were proved in patients with IBD and anemia.

The effectiveness of this method showed the normalization of hemoglobin in 68% of patients within 3 months. In contrast, intravenous iron administered during the inpatient treatment period was not sufficiently effective in this category of patients, which required the continuation of outpatient therapy with preparations of Sucrosomial® iron.

Based on the obtained data and international experience, there was formulated and substantiated the algorithm of differentiated therapy of IDS in patients with a mild form of IBD.

Keywords: Iron Deficiency; Iron Deficiency Syndrome; Inflammatory Bowel Disease; Treatment of Anemia; Sucrosomial® Iron; Intravenous Iron

Abbreviations

ACD: Anemia of Chronic Disease; CD: Crohn's Disease; CIC: Circulating Immune Complexes; CRP: C-Reactive Protein; EPO: Endogenous Erythropoietin; ERS: Erythrocyte Sedimentation Rate; Hb: Hemoglobin; HIP: Hypoxia Induced Factor; HP: Hepcidin; IBD: Inflammatory Bowel Disease; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; IDS: Iron Deficiency Syndromes; IU: International Units; LIBC: Latent Iron Binding Capacity; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; MCSC: Loginov Moscow Clinical Scientific Centre; Rh-EPO: Recombinant Human Erythropoietin; RBC: Erythrocytes; SI: Serum Iron; SF: Serum Ferritin; TIBC: Total Iron Binding Capacity; TF: Transferrin; TSI: Transferrin Saturation With Iron; U: Mann-Whitney Test; UC: Ulcerative Colitis; WHO: World Health Organization.

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Introduction

One of the most frequent and serious extraintestinal manifestations of inflammatory bowel diseases (IBD) is anemia [1,2]. It significantly affects patients’ quality of life and reflects the disease morbidity and activity [3,4]. The frequency of anemia depends on the severity and activity of the inflammatory process [3,5].

The leading cause of anemia development is iron deficiency (ID), which is observed more often than anemia [6,7]. The absolute ID formation is associated with malabsorption during small bowel inflammation in patients with Crohn’s disease (CD), and post-hemorrhagic nature of anemia associated with large bowel affection during ulcerative colitis (UC) [8-10]. However, the leading role in the development of anemia and other redistributive variants of ID belongs to chronic inflammation, which determines IBD pathogenesis [11-13]. All these types of anemia develop as a result of iron deficiency erythropoiesis, are hypo-normochromic or micro-normocytic anemias according to their morphological characteristics and are called iron deficiency syndromes (IDS). They are characterized by low values of serum iron (SI) and transferrin saturation coefficient (TSI) [14]. In case of absolute ID with a low serum ferritin index (SF < 30 μg/L), anemia is considered iron deficiency anemia (IDA) and requires iron preparations administration [14-16]. When a high level of inflammation markers, inadequate production of endogenous erythropoietin (EPO) and SF indices of more than 100 μg/L are detected, such conditions are called anemia of chronic disease (ACD). Such IDS variant, first of all, requires anti-inflammatory therapy, the effectiveness of which will determine the success of hemoglobin correction [12,17].

At present, the role of absolute and functional ID in anemia development has not been completely determined, and the ratio and combination of various forms of IDS in patients with IBD have not been clarified. This is the reason for the lack of adequate, effective and safe anemia treatment methods in this category of patients.

In clinical practice, both iron and recombinant human erythropoietin (rh-EPO) preparations are used. At the same time, oral supplements are poorly tolerated, while intravenous preparations exacerbate the course of the inflammatory process, are not routinely prescribed, and have a large number of restrictions on their use [14,16,18]. Rh-EPO preparations require mandatory patient examination to exclude a different type of anemia, studies of EPO content are used for iron-resistant anemia, and are expensive [12,14,17,19-21].

Recent publications presented the successful use of a new oral Sucrosomial® form of iron in various IDS treatment. This is due to the unique ability of absorption throughout the small bowel and with partial control by hepcidin, which ensures high effectiveness and safety. In addition, the preparation allows to offer patients with IBD an optimal daily dose, which equals to 60 mg of elemental iron [22,23].

All these factors make it necessary to decide on the need for scientific work to study IDS characteristics in case of IBD, assess the effectiveness and tolerability of the oral Sucrosomial® form of iron, and compare its effectiveness with standard treatment with intravenous iron preparations.

Purpose of the Study

The purpose of study is to identify peculiarities of IDS in case of IBD for adequate pathogenetic treatment with iron preparations, characterize IDS in case of IBD by morphological parameters, iron metabolism, inflammation and hypoxia markers, study the effectiveness and tolerability of the oral Sucrosomial® form of iron in patients having IBD with anemia, assess the results of intravenous ferrotherapy in patients having IBD with anemia and compare the effectiveness of oral therapy and intravenous iron preparations in this group of patients.

Materials and Methods

The study included 77 patients with proven IBD and anemia, hospitalized in the Department of Inflammatory Bowel Diseases of the Bowel Pathology Department of Loginov Moscow Clinical Scientific Center (MCSC). The study was approved by the Ethics Committees of MCSC and Peoples’ Friendship University of Russia. Diagnoses of UC or CD were confirmed using colonoscopy, irrigoscopy, x-ray examina-
Anemia was determined according to World Health Organization (WHO) criteria: a decrease in hemoglobin (Hb) concentration less than 13 g/dL in men and less than 12 g/dL women.

**Inclusion criteria**
- Proven IBD diagnosis;
- Anemia;
- No iron preparations therapy over the past 6 months.

**Exclusion criteria:**
- Severe form of IBD.
- Severe anemia (Hb < 7 g/dL according to WHO criteria), acute post-hemorrhagic anemia.
- Hyperchromic macrocytic anemia with mean corpuscular hemoglobin (MCH) above 32 pg and mean corpuscular volume (MCV) above 100 fL.
- Proven malignant tumor diseases, chronic renal failure, blood diseases.

**Patients were divided into 3 groups:**
- **Group I:** 27 patients to determine anemia characteristics - diagnosis (UC: 15, CD: 12), median age ± standard deviation (41.1 ± 13.8 years), gender (men - 12, women - 16).
- **Group II:** 28 patients to evaluate the effectiveness of oral Sucrosomial® iron - diagnosis (UC: 14, CD: 14), median age ± standard deviation (43.5 ± 13.5 years), gender (men - 8, women - 20).
- **Group III:** 22 patients to evaluate the effectiveness of intravenous ferrotherapy with iron (III) hydroxide sucrose complex: diagnosis (UC: 15, CD: 7), median age ± standard deviation (37.3 ± 13.1 years), gender (men - 12, women - 10).

The last two groups were used to compare the effectiveness of oral iron treatment vs intravenous iron preparations.

**Laboratory assays**
- Erythrocyte indices: Hb (g/dL), erythrocytes (RBC, ×10¹²/L), MCH (pg), MCV (fL), erythrocyte sedimentation rate (ESR, mm/hour).
- Iron metabolism markers: Serum iron (SI, µmol/L), transferrin (TF, g/L), serum ferritin (SF, µg/L), total iron binding capacity (TIBC, µmol/L), latent iron binding capacity (LIBC, µmol/L), transferrin saturation with iron (TSI,%).
- B vitamins: B₁₂ (pg/L), B₉ (ng/L).
- Inflammation markers: Circulating immune complexes (CIC, units), hepcidin (HP, pg/ml), c-reactive protein (CRP, mg/l).
- Hypoxia markers: Hypoxia induced factor (HIF, pg/ml), endogenous EPO, (IU/ml).

**Questionnaire**
To assess the tolerability of oral Sucrosomial® iron the severity of IBD symptoms was investigated. Patients were asked to fill out a questionnaire, which reflected 5 major complaints related to gastrointestinal tract (GIT) dysfunction: nausea and vomiting, abdominal pain, constipation, diarrhea, blood in the stool and black stool. Data were recorded before treatment, 1 month and 3 months after treatment. Patients rated every item from 1 (absence or minimal complaints) to 5 (maximum complaints) points. Then, the mean values for each symptom and for the general group of symptoms were calculated and compared with each other at different stages of treatment.
Study design

To study IDS laboratory characteristics in IBD, such as erythrocyte indices, iron metabolism, inflammation markers and hypoxia markers, laboratory data of 27 patients (Group I) with SF of less than 30 μg/L, SF between 30 and 100 μg/L and SF of more than 100 μg/L were analyzed.

To study the effectiveness and tolerability of oral Sucrosomial® iron in IBD patients with anemia, 28 patients with SF of less than 100 μg/L were selected (Group II). These patients signed the informed consent, and then received 1 capsule of Sucrosomial® iron (30 mg of elemental iron per capsule) twice daily for 3 months. Before treatment and after 1 and 3 months following treatment, they underwent blood tests and filled out a questionnaire. The study was conducted prospectively. Study results of questioning were obtained for 20 out of 28 patients.

To assess the laboratory results of intravenous ferrotherapy in IBD patients with anemia, 22 patients with SF of less than 100 μg/L were selected (Group III). These patients received a dose of 100 mg of intravenous iron per injection daily while they were in the hospital, reaching a cumulative dose of 500 to 1300 mg. The mean intravenous iron dose was 913.6 ± 269.6 mg. Before the treatment and 3 months after the release, the results of their primary and control laboratory tests were examined. The study was conducted retrospectively.

All patients receiving oral and intravenous iron therapy were simultaneously prescribed anti-inflammatory treatment with mesalazine (or sulfasalazine), azathioprine, or glucocorticosteroids (GCS).

In order to assess the effectiveness of oral Sucrosomial® iron, laboratory test results for Group II and Group III (erythrocyte indices, iron metabolism and inflammation markers) were explored.

Statistical analysis

Mean value (M), standard deviation (σ), and error of the mean were calculated. The results were presented as M ± σ. Statistical difference was calculated using the Mann-Whitney test (U). The difference was considered as statistically significant at p ≤ 0.05.

Results and Discussion

When calculating the ratio of patients with iron deficiency and patients with its deposition (Group I), it was observed that 23 (85%) IBD patients with anemia have ID (SF < 100 μg/L), 21 (78%) have absolute deficiency (SF < 30 μg/L) and only 4 (15%) have in excess (SF > 100 μg/L). Groups with different SF content did not differ in Hb parameters. Its concentration was 10.6 ± 1.5 g/dL, 9.1 ± 2.0 g/dL, 9.6 ± 1.9 g/dL, respectively. Erythrocyte indices, iron metabolism and vitamin B levels in the indicated subgroups are presented in table 1, and markers of inflammation and hypoxia in table 2.

<table>
<thead>
<tr>
<th>SF</th>
<th>N (%)</th>
<th>Erythrocyte Indices</th>
<th>Iron Metabolism</th>
<th>Vitamins B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 μg/L</td>
<td>21 (78%)</td>
<td>MCH = 25.2 ± 3.8*</td>
<td>SI = 7.4 ± 6.4*</td>
<td>B_{12} = 338.8 ± 271.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCV = 80.8 ± 6.4</td>
<td>TSI = 9.0 ± 3.6*</td>
<td>B_{9} = 9.1 ± 0.6</td>
</tr>
<tr>
<td>30 - 100 μg/L</td>
<td>2 (7%)</td>
<td>MCH = 27.2 ± 1.0*</td>
<td>SI = 3.8 ± 1.8*</td>
<td>B_{12} = 140 ± 28.3*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCV = 74.4 ± 8.3*</td>
<td>TSI = 7.2 ± 5.5*</td>
<td>B_{9} = 9.1 ± 0.6</td>
</tr>
<tr>
<td>&gt; 100 μg/L</td>
<td>4 (15%)</td>
<td>MCH = 24.3 ± 2.5*</td>
<td>SI = 17.8 ± 17.0</td>
<td>B_{12} = 387.5 ± 369.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCV = 77.6 ± 9.5*</td>
<td>TSI = 31.5 ± 30.9</td>
<td>B_{9} = 18.3 ± 19.4**</td>
</tr>
</tbody>
</table>

Table 1: Erythrocyte indices, iron metabolism and vitamin B according to serum ferritin content.

Abbreviations: n (%), number (percentage) of participants in the specified category; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; SI: Serum Iron; SF: Serum Ferritin; TSI: Transferrin Saturation With Iron.

Note: *: Mean value is below normal; **: Mean value is above normal; Normal values: MCH (28 - 32 pg), MCV (80 - 100 fl), SI (10 - 25 μmol/L), TSC (20 - 35%), B_{12} (300 - 800 pg/L), B_{9} (4 - 14 ng/L).

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Data in table 1 show that, regardless of SF content, all anemias are of hypochromic microcytic nature, thus it is impossible to judge the degree and nature of ID by erythrocyte measures in case of IBD. In subgroups with ID (SF < 100 µg/L), symptoms of impaired iron metabolism were revealed: low levels of SI and TSI, which proved the existence of iron-deficiency erythropoiesis in such anemias. On the contrary, when SF content was higher than 100 µg/L, mean values of SI and TSI corresponded to normal values, thus, the reason for the development of anemia with high SF was different from that with low one.

To discuss other reasons for the development of anemias in IBD, it is necessary to assess the results for markers of inflammation and hypoxia, defined in the three abovementioned subgroups (Table 2). According to the data obtained, regardless of the degree of iron deficiency (i.e. SF amount), high mean values of inflammation markers were revealed in all subgroups. Thus, no true absolute IDA was actually revealed in any group, but all IDS had symptoms of ACD.

### Table 2: Markers of inflammation and hypoxia according to serum ferritin content

<table>
<thead>
<tr>
<th>Sf</th>
<th>N (%)</th>
<th>Inflammation Markers</th>
<th>Hypoxia Markers</th>
</tr>
</thead>
</table>
| < 30 µg/L   | 21 (78%) | ESR = 26 ± 16 **  
  CIC = 194.9 ± 81.4**  
  HP = 165.2 ± 206.1** | HIF = 10.6 ± 7.5**  
  EPO = 47.6 ± 88.4** |
| 30 - 100 µg/L | 2 (7%) | ESR = 56 ± 9.9**  
  CIC = 220 ± 70.7**  
  HP = 26.5 ± 0.7 | HIF = 3.3 ± 0.8  
  EPO = 26.5 ± 8.5 |
| > 100 µg/L  | 4 (15%) | ESR = 38 ± 18.3**  
  CIC = 200 ± 57.2**  
  HP = 242.5 ± 165.8** | HIF = 11.5 ± 7.2**  
  EPO = 4.8 ± 1.4* |

**Abbreviations:** n (%): Number (percentage) of participants in the specified category; CIC: Circulating Immune Complexes; EPO: Endogenous Erythropoietin; ESR: Erythrocyte Sedimentation Rate; HP: Hepcidin; HIF: Hypoxia Induced Factor; SF: Serum Ferritin.

**Note:** *: Mean value is below normal; **: Mean value is above normal. Normal values: ESR (2 - 15 mm/h), CIC (< 120 units), HP (40 - 80 pg/mL), HIF (< 5 pg/mL), EPO (8 - 20 IU/mL).

Interesting results were obtained by analyzing the hypoxia markers, where no effects of anemia on the body were detected in the group with normal SF indices (from 30 to 100 µg/L). This could prove high adaptive ability of such category of patients (however, they are only 2 patients). The remaining 25 patients (93%), either with ID or with SF>100 µg/l, experienced a pronounced effect of hypoxia, which was proved by a high HIF mean value, requiring mandatory therapeutic measures to correct anemia.

The most interesting relationship was found in the observation of endogenous erythropoietin production. It turned out that the lower SF correlate with higher endogenous erythropoietin synthesis (Figure 1). In patients with high SF level (15% of cases) we discovered inadequate erythropoietin production in relation to anemia severity, and there were no changes in iron metabolism parameters. Therefore in this Iron Deficiency Syndromes variant, iron preparations would probably have no effect, but on the contrary could have negative effects by activation of lipid peroxidation and exacerbating the inflammatory process.

In all subgroups of examined patients with various SF levels high markers of inflammation were revealed, which required mandatory adequate anti-inflammatory therapy to be combined with iron preparations when SF is less than 100 µg/L, that is in 85% of patients with anemia and IBD. In patients with a high SF level (15% of patients) anemia treatment should be started with anti-inflammatory preparations, and in the absence of an increase in of Hb a recombinant human erythropoietin (rh-EPO) would be indicated for them.
To study the effectiveness of treatment with Sucrosomial® iron, a comparison of erythrocyte indices (Table 3) and iron metabolism (Table 4) was made in the group of IBD patients with anemia during 3 months of therapy (Group II). Considering that the treatment was carried out together with constant anti-inflammatory therapy, measures of inflammation markers were consistently studied along with other laboratory tests (Table 5).

Data in table 3 show that there was a dynamic increase of all erythrocyte indices, and the treatment effectiveness met WHO criteria with respect to Hb parameters. That is, after a month of therapy, an increase in the mean hemoglobin values over 10 g/L was achieved, and after 3 months, Hb levels normalized. In addition to Hb, there was almost full normalization of mean MCH and full normalization of mean MCV. The most rapid and significant effect was seen in Hb level increase (one month after treatment initiation). Over the next two months, Hb, MCH and MCV levels significantly raised, and at the end of oral Sucrosomial® iron supplementation, all the erythrocyte indices statistically increased. This finding proves that this innovative oral iron is highly effective in treating anemia in IBD patients, while other oral preparations proved to be extremely ineffective.

Table 3: Erythrocyte indices during therapy with oral Sucrosomial® iron.

**Abbreviations:** Hb: Hemoglobin; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; RBC: Erythrocytes; U: Mann-Whitney Test.
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Considering the results of changes in iron metabolism (Table 4), a statistically significant increase in SI at all stages of treatment was detected, which was likely to cause an increase in all erythrocyte indices and hemoglobin normalization. After 3 months of treatment, normalization and a statistically significant decrease in TIBC were established, which allowed us to consider a full ID compensation during Sucrosomial® iron treatment. The dynamic increase of TSI and SF as the main markers of body iron deposits was also noted, however those measures did not reach normal values requiring longer treatment with iron preparations. According to table 5, normalization of CRP levels, a statistically significant decrease in CRP and ESR were revealed, which indicated an effective anti-inflammatory treatment.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Before Treatment</th>
<th>After 1 Month</th>
<th>After 3 Months</th>
<th>U-test (p value) Before/After 1 Month</th>
<th>U-test (p value) After 1/3 Month(s)</th>
<th>U-test (p value) Before/After 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI (µmol/L)</td>
<td>4.5 ± 2.2</td>
<td>7.7 ± 6.0</td>
<td>10.1 ± 4.4</td>
<td>256 (p &lt; 0.05)</td>
<td>230.5 (p &lt; 0.01)</td>
<td>108 (p &lt; 0.01)</td>
</tr>
<tr>
<td>TIBC (µmol/L)</td>
<td>66.1 ± 11.5</td>
<td>63.9 ± 8.7</td>
<td>58.7 ± 12.4</td>
<td>-</td>
<td>-</td>
<td>239 (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

Table 4: Iron metabolism markers during treatment with oral Sucrosomial® iron (only statistically significant values are indicated).

**Abbreviations:** SI: Serum Iron; TIBC: Total Iron Binding Capacity; U: Mann-Whitney test.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Before Treatment</th>
<th>After 1 Month</th>
<th>After 3 Months</th>
<th>U-test (p value) Before/After 1 Month</th>
<th>U-test (p value) After 1/3 Month(s)</th>
<th>U-test (p value) Before/After 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>10.7 ± 18.0</td>
<td>5.7 ± 6.0</td>
<td>3.1 ± 3.6</td>
<td>-</td>
<td>-</td>
<td>253.5 (p &lt; 0.05)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>28.6 ± 13.7</td>
<td>16.5 ± 8.3</td>
<td>17.7 ± 12.7</td>
<td>145 (p &lt; 0.01)</td>
<td>-</td>
<td>151 (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

Table 5: Inflammatory markers during therapy with oral Sucrosomial® iron (only statistically significant values are indicated).

**Abbreviations:** CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; U: Mann-Whitney Test.

Tolerability of Sucrosomial® iron is presented in table 6. According to the data obtained, a dynamic decrease in the average severity of all complaints of GIT dysfunction, as well as a statistically significant decrease in total GIT complaints (U = 117.5, p < 0.05) and diarrhea symptoms after 1 month (U = 129, p = 0.05) and 3 months (U = 112, p < 0.05). Not a single patient interrupted the course and refused treatment. Measures obtained indicate high tolerability and safety of Sucrosomial® iron.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mean value (from 1 to 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>General complaints for GIT dysfunction</td>
<td>2.1 ± 0.8</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.5 ± 1.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td>Blood in the stool, black stool</td>
<td>2.0 ± 1.3</td>
</tr>
</tbody>
</table>

Table 6: Symptoms of gastrointestinal tract dysfunction during treatment with oral Sucrosomial® iron.

To compare the effectiveness of oral Sucrosomial® and intravenous iron, erythrocyte indices, iron metabolism, and inflammation markers were studied before and after 3 months of iron (III) hydroxide sucrose complex treatment (Group III). According to the data obtained,
there was a positive increase in erythrocyte indices (Table 7). There was a statistically significant increase in Hb and RBC, however mean Hb levels did not reach normal values, and after 3 months of treatment erythrocyte hypochromia still persisted. The lack of MCH normalization indicated a continuing iron deficiency for adequate synthesis of hemoglobin in erythrokaryocytes.

<table>
<thead>
<tr>
<th>Indices</th>
<th>Before treatment</th>
<th>After 3 months</th>
<th>U-test (p value) Before/After 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>100.1 ± 15.6</td>
<td>115.7 ± 17.4</td>
<td>115 (p &lt; 0.01)</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>25.8 ± 2.7</td>
<td>26.6 ± 4.1</td>
<td>-</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>81.9 ± 6.0</td>
<td>84.4 ± 7.3</td>
<td>-</td>
</tr>
<tr>
<td>RBC (x10¹²/L)</td>
<td>4.1 ± 0.6</td>
<td>4.5 ± 0.6</td>
<td>124.5 (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

Table 7: Erythrocyte indices during the therapy with intravenous iron.

Abbreviations: Hb: Hemoglobin; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; RBC: Erythrocytes; U: Mann-Whitney Test.

Investigating the content of SI and markers of inflammation (CRP) (Table 8), we obtained data on good effectiveness of anti-inflammatory therapy and ID decrease. However, despite a statistically significant decrease in CRP after 3 months of treatment, its content was still higher than normal values. As for SI level, no significant increase was observed, which indicated the lack of effectiveness of intravenous iron preparations, considering that they were used in a single hospitalization. Given a positive response with respect to Hb concentration, most likely, in order to achieve a better effect when using intravenous iron preparations, patients would need a repeated hospitalization within 3 months of treatment, in order to re-examine iron deposits and continue intravenous ferrotherapy, or they should be switched to oral Sucrosomial® iron after discharge from the hospital.

<table>
<thead>
<tr>
<th>Indices</th>
<th>Before Treatment</th>
<th>After 3 Months</th>
<th>U-test (p value) Before/After 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI (µmol/L)</td>
<td>5.4 ± 5.4</td>
<td>7.9 ± 6.1</td>
<td>-</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>27.4 ± 42.1</td>
<td>7.6 ± 13.2</td>
<td>155 (p &lt; 0.05)</td>
</tr>
</tbody>
</table>

Table 8: Iron metabolism and markers of inflammation during the therapy with intravenous iron.

As for erythrocyte indices and Hb, RBC, SI and CRP levels, no differences were observed between Group II and Group III. However, after 3 months of treatment, Group II managed to get normal mean Hb values (124.9 ± 14.1 g/L), while in Group III those values reached only 115.7 ± 17.4 g/L. As a result of treatment, 19 of 28 patients (68% of cases) in Group II reached normal Hb values. In Group III, Hb was normalized only in 4 out of 22 patients (18% of cases). Thus, the effectiveness of oral Sucrosomial® iron, which can be administered continuously during both inpatient and outpatient treatment stages, was significantly higher than intravenous one, limited only to the inpatient stage.

A scheme for treatment of IDS in case of IBD is showed in figure 2. According to it, for SF less than 100 µg/L, treatment with iron preparations was indicated. In case of severe anemia, considering available literature data and recommendations, treatment with intravenous iron preparations was indicated; for non-severe and moderate anemia, according to our data, treatment with oral Sucrosomial® iron would be a better option. After discharge from the hospital patients with severe anemia should be switched to oral administration of Sucrosomial® iron as a safe and effective way to recover ID. In case of SF of more than 100 µg/L, iron therapy was not indicated; depending on the severity of anemia, wait-and-see tactics, therapy with rh-EPO or erythrocyte concentrate transfusion (in severe anemia) could be considered. In all cases, antianemia treatment should be carried out along with anti-inflammatory IBD treatment.
**Figure 2:** Treatment scheme for iron deficiency syndromes in non-severe inflammatory bowel disease.

**Abbreviations:** IBD: Inflammatory Bowel Disease; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; Hb: Hemoglobin; SF: Serum Ferritin; hr-EPO: Recombinant Human Erythropoietin.

**Conclusion**

In our study IDS in case of IBD were IDA+ACD in 85% and ACD in 15% of patients, respectively. The routine administration of iron preparations in anemia treatment of patients with IBD was not indicated without SF determination.

High effectiveness and tolerability of the oral form of Sucrosomial® iron were proved by normalization of mean Hb values, laboratory indices (p < 0.01), reduction of clinical IBD symptoms and statistically significant decrease in total GIT complaints (p < 0.05) in patients with SF of less than 100 μg/L.

Therapy with intravenous iron preparations had significant effectiveness but was contraindicated in 15% of patients with IBD and was insufficient for full Hb normalization. Further re-hospitalization and continuation of intravenous therapy or switching patients to oral iron was required to achieve target measures of erythrocyte and iron status.

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New Options in Management of Iron-Deficiency Syndromes in Inflammatory Bowel Diseases

Oral Sucrosomial® iron preparations were able to normalize Hb in 68% of patients, which was more than in case of intravenous ferrotherapy (18%), however 3-months treatment might not be enough to fully normalize body’s iron deposits.

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