The Effectiveness of Ferric Carboxymaltose on the Improvement of Chronic Iron Deficiency Anemia in Patients With Colon Cancer: A Controlled Randomized Clinical Trial

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Abstract

Background: Anemia is prevalent in 32% to 60% of patients with cancer due to an underlying disease, nutritional deficiencies and complications of medication used in chemotherapy. National comprehensive cancer network (NCCN) recommends the use of oral or intravenous iron supplementation in patients with iron deficiency anemia.

Objectives: The current study aimed to determine the effectiveness of ferric carboxymaltose to improve the chronic iron deficiency anemia in patients with stage III/IV colon cancer compared with that of oral iron therapy.

Methods: The study was a controlled randomized clinical trial performed on patients with stage III/IV colon cancer referred to the Rasoul-Akram hospital in Tehran, Iran, in 2015. Hemoglobin levels less than 13 g/dL in males and less than 12 g/dL in females, ferritin levels less than 30 µg/L, serum iron levels less than 50 µg/dL and total iron binding capacity (TIBC) levels less than 360 µg/dL are considered as chronic iron deficiency anemia. Patients with stage III/IV colon cancer and chronic iron deficiency anemia were enrolled. Non-compliance with the treatment regimen, intolerable side effects and lack of follow-up were the measures of exclusion from the study. Patients were selected based on the block balanced randomization and divided into two groups. The first group received the standard treatment of oral ferrous sulfate (65 mg three times a day for two months), and the second group received injection vials of ferric carboxymaltose (1500 mg for patients weighing less than 70 kg, 2000 mg for more than 70 kg).

Results: Ten patients (five in the first group and five in the second group) were excluded due to lack of follow-up tests. In each group, 30 patients were considered in the final analysis. Analysis showed that patients who received ferric carboxymaltose had higher levels of hemoglobin and ferritin compared to patients who received ferrous sulfate (P = 0.000). The results showed that increased levels of hemoglobin in iron sulfate had no significant differences regarding gender (male or female) and the stage of the disease; although in the carboxymaltose group, improved levels of hemoglobin were significantly better in females than males (P = 0.034). Also, the level of ferritin in iron sulfate group showed a better increase in females compared to males (P = 0.007).

Conclusions: Findings of the study showed that using the parenteral iron formulation of carboxymaltose had an excellent efficacy in improving iron deficiency anemia in patients with high rates of colon cancer compared with that of oral ferrous sulfate. This effect is mostly related to the proper formulation of ferric carboxymaltose, which results in a stable and continuous increase in the levels of ferritin and hemoglobin in patients.

Keywords: Iron Deficiency Anemia, Colon Cancer, Iron Injections, Oral Iron, Ferric Carboxymaltose, Ferrous Sulfate

1. Background

The world health organization (WHO) defines low blood levels of hemoglobin less than 13 g/dL in males, less than 12 g/dL in females and less than 10 g/dL during pregnancy as anemia (1, 2). Iron deficiency is usually the main cause of anemia (3, 4). There is an iron deficiency in chronic diseases such as chronic kidney disease; the etiology in such cases is often related to multiple organ dysfunctions in the absorption of oral ferrous sulfate (5). Also, conditions such as malnutrition, increased iron requirements (e.g. pregnancy), acute or chronic blood loss (vaginal bleeding, gastrointestinal bleeding, blood loss during surgery and cancer of the digestive tract), chronic infec-
tions and poor absorption of iron are some of the causes of iron deficiency (5, 6).

Hepcidin, a 25-amino acid peptide, is the primary regulator of iron homeostasis. Hepcidin serum levels increases in chronic inflammations such as cancer and autoimmune diseases, and can cause anemia. Other factors involved in the regulation of the hepcidin are erythropoiesis and hypoxia (7). Iron deficiency occurs in two forms of absolute or functional. In absolute iron deficiency, the iron supply of body is weak, and there is no iron to synthesize hemoglobin. Whereas in functional iron deficiency, body iron stores are normal or even increase but there is a dysfunction in releasing them to fulfill the needs of the body. The proper treatment is to correct anemia and iron deficiency by replacing iron stores in patients (7, 8).

Ferric carboxymaltose is a colloidal solution of polynuclear ferric hydroxide (trivalent), which is stabilized by carbohydrate polymer of carboxymaltose. Ferric carboxymaltose has an isotonic osmolarity and pH of 4.5 - 7.0 (9). The molecular structure of ferric carboxymaltose is designed in such a way that it causes the entrapment of iron in macrophages of the reticuloendothelial system in the liver, spleen and bone marrow; therefore, iron is available for the transferrin protein. This process prevents releasing large amounts of iron ions into the serum (10-13).

Due to the underlying disease and chemotherapy in patients with cancer, anemia is common in 32% - 60% of such patients. National comprehensive cancer network (NCCN) recommends the use of oral or intravenous iron supplementation in patients with absolute iron deficiency (ferritin less than 30 ng/mL and transferrin saturation less than 20%). In patients with functional iron deficiency (ferritin 30 - 800 ng/mL and 20% - 50% transferrin saturation) who receive erythropoiesis-stimulating drugs, intravenous iron is recommended (14).

Treatment of iron deficiency anemia in patients with colon cancer can prevent complications due to underlying disease or chemotherapy (15, 16).

2. Objectives

The current study aimed to determine the effectiveness of ferric carboxymaltose in the improvement of chronic iron deficiency anemia in patients with stage III/IV colon cancer compared with that of oral iron therapy.

3. Methods

The study was a controlled randomized clinical trial performed on patients with stage III/IV colon cancer referred to the Rasoul-Akram hospital in Tehran, Iran, in 2015. Of the 70 patients participating in the study, 10 patients (five in the first group and five in the second group) were excluded due to lack of follow-up tests (view 1). Ultimately, 30 patients in each group were considered in the final analysis. The comparison between the two groups regarding age, gender, stage of disease, as well as data of pre-study test results revealed the homogeneity of the two groups (Table 1). After the intervention, differences in hemoglobin and ferritin levels before and after drug administration showed significant differences in both groups (Table 2). Results showed that patients who received ferric carboxymaltose had higher hemoglobin and ferritin levels compared...
to patients who received ferrous sulfate \( (P = 0.000) \) (Figures 2 and 3).

Changes in hemoglobin levels in patients were studied according to gender and stage of the disease. The results showed no significant increase in the hemoglobin levels in ferrous sulfate treatment based on gender and the disease stage. However, with ferric carboxymaltose, improvement in hemoglobin levels were significantly better in females than males \( (P = 0.034) \). Also, in the level of ferritin, females showed a better change after treatment with ferrous sulfate than males \( (P = 0.007) \).

No serious side effects were observed regarding the employed medication.

5. Discussion

Many researchers studied intravenous iron treatment of chronic iron deficiency anemia. However, the literature on the use of ferric carboxymaltose in chronic diseases, especially on patients with cancer is limited. In the current study the treatment of iron deficiency anemia in patients with colon cancer was examined. Fast and proper result was observed at the ferric carboxymaltose group. The improvement after the use of one or two doses of carboxymaltose was significant; therefore, at the end of the experiment, ferritin level in the carboxymaltose group was 9.2 times more than that of the oral treatment group.

In the study, in both groups, females showed better health outcomes than males regarding hemoglobin and ferritin levels. In the ferric carboxymaltose group, hemoglobin levels were significantly improved in females. Also, in the oral treatment group changes in serum ferritin level was significantly better in females than males \( (P = 0.007) \). This reflects the greater sensitivity of females and a better response to any treatment of anemia, especially after treatment with ferric carboxymaltose. It should be noted that in none of the patients in the oral treatment group the serum ferritin level reached normal levels. While all patients in the second group had a normal ferritin level at the end of the treatment.

The study by Hedenus et al. (8) on patients with lymphoid malignancies treated by chemotherapy drugs also reported significant changes in hemoglobin and ferritin levels in the group receiving ferric carboxymaltose compared to the control group. Another notable detail in the study was that ferritin levels increased before an increase in hemoglobin level. The significant increase in ferritin levels occurred in the second week after drug administration, but hemoglobin levels increased significantly in the eighth week of treatment. In the current study, ferritin levels in the second week were about 12 times more than the pre-test levels, while hemoglobin concentration was significantly lower. According to similar studies, it was expected that hemoglobin levels increased in the following weeks.

Steinmetz et al. (17) in Germany used ferric carboxymaltose to treat iron deficiency anemia caused by cancer or chemotherapy. Also in the current study, changes in hemoglobin and ferritin levels were investigated to evaluate the efficacy of ferric carboxymaltose treatment. Changes in the average level of hemoglobin in carboxymaltose treatment were 1.4 g/dl, while in the group taking a erythropoietin-stimulating drug and carboxymaltose at the same time, the difference was 1.6 g/dl but the difference was not statistically significant. The researchers concluded that patients with a hemoglobin level less than 11 g/dl and serum ferritin less than 500 ng/ml get the best results from carboxymaltose treatment. In the present study, patients had low levels of hemoglobin and ferritin in their serum, and in all cases, a significant improvement was achieved.

In most of the other studies, treatment with ferric carboxymaltose was compared to blood transfusions or oral iron treatment. In some literatures, the need for blood transfusions despite treatment with oral or injectable iron as the standard treatments of anemia were studied (18, 19). The study by Athibovonsuk et al. (19), comparatively investigated the effects of intravenous and oral treatments in patients with gynecological cancer receiving chemotherapy. After each session of chemotherapy, one iron injection or three oral doses of iron a day were administered for two groups of 32 patients. At the end of chemotherapy period, 28% of the first group and 56% of the second group needed blood transfusions. Quicker recovery of serum levels of hemoglobin and ferritin in patients were also confirmed in this study.

The current study results, showed a noteworthy recovery of ferritin, despite the likelihood of a significant increase in hemoglobin within the eight-week follow-up. Still, the exact dose of ferric carboxymaltose for iron deficiency anemia should be clarified, especially in severe or different malignancies receiving chemotherapy regimens in patients with cancer.

In conclusion, according to the obtained results, it was concluded that intravenous formulation of ferric carboxymaltose has an excellent efficacy to improve iron deficiency anemia in patients with high rates of colon cancer compared with that of oral treatments. This effect is mainly related to drug formulation of ferric carboxymaltose, which results in a stable and sustained increase in the levels of ferritin and hemoglobin in patients.
### Table 1. Demographic Data of the Subjects in the Study Groups\(^a, b\)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ferrous Sulfate Group</th>
<th>Ferric Carboxymaltose Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.87 ± 13.28</td>
<td>58.50 ± 12.13</td>
<td>0.621</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>19</td>
<td>0.598</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cancer stage (III/IV)</td>
<td>22/8</td>
<td>22/8</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.42 ± 1.60</td>
<td>9.60 ± 1.68</td>
<td>0.057</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>9.85 ± 5.59</td>
<td>8.03 ± 3.78</td>
<td>0.146</td>
</tr>
</tbody>
</table>

\(^a\)Data were analyzed by T-test and Chi-square test and expressed as mean ± SD.
\(^b\)The significance level was considered < 0.05.

### Table 2. Comparison of HB and Ferritin Levels Pre- and Post-treatment Between the Groups\(^a, b\)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P Value</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>10.42 ± 1.60</td>
<td>11.67 ± 1.28</td>
<td>0.001</td>
<td>9.85 ± 5.59</td>
<td>12.27 ± 4.20</td>
<td>0.000</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>9.60 ± 1.68</td>
<td>13.86 ± 0.74</td>
<td>0.000</td>
<td>8.03 ± 3.78</td>
<td>113.40 ± 32.05</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Abbreviation: HB, hemoglobin.

\(^a\)Data were analyzed by paired t-test and expressed as mean ± SD.
\(^b\)The significance level was considered < 0.05.

### Table 3. Pre- and Post-Treatment Differences of HB Level Based on Gender and Cancer stages Between the Groups\(^a, b\)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
<th>Cancer Stage</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>0.45</td>
<td>0.24</td>
<td>0.104</td>
<td>III</td>
<td>0.77</td>
<td>0.27</td>
<td>0.66</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>3.75</td>
<td>1.45</td>
<td>0.034</td>
<td>IV</td>
<td>4.16</td>
<td>1.90</td>
<td>4.54</td>
</tr>
</tbody>
</table>

\(^a\)Data were analyzed by t-test and expressed as mean ± SD.
\(^b\)The significance level was considered < 0.05.

### Table 4. Pre- and Post-treatment Differences of Ferritin Level Based on Gender and Disease Stage Between the Groups\(^a, b\)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
<th>Cancer Stage</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>1.41</td>
<td>3.73</td>
<td>0.007</td>
<td>III</td>
<td>2.57</td>
<td>2.09</td>
<td>2.40</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>102.95</td>
<td>27.34</td>
<td>0.598</td>
<td>IV</td>
<td>106.50</td>
<td>35.33</td>
<td>102.25</td>
</tr>
</tbody>
</table>

\(^a\)Data were analyzed by t-test and expressed as mean ± SD.
\(^b\)The significance level was considered < 0.05.
Figure 1. Participants’ Flow Diagram
Figure 2. Comparing Hemoglobin Level Pre- and Post-Treatment Between the Groups

Figure 3. Comparing Ferritin Level Pre- and Post-Treatment Between the Groups

References

17. Steinmetz T, Tschechne B, Harlin O, Klement B, Franzem M, Wamhoff J, et al. Clinical experience with ferric carboxymaltose in the treat-
