Efficacy of Combination of Iron Pyrophosphate and Folic Acid in Management of Iron Deficiency- A Retrospective Study

Sejal Modi*

Mothers’ Maternity and Nursing Home, Ahmedabad, India

*Corresponding Author: Sejal Modi, Mothers maternity and nursing home, Ahmedabad, India, E-mail: shiv_kaumil@yahoo.com

Citation: Sejal Modi. Efficacy of Combination of Iron Pyrophosphate and Folic Acid in Management of Iron Deficiency- A Retrospective Study. ERWEJ. 2022;2(1):21-31. 10.54136/ERWEJ-0201-10019

© Author(s), 2022. Publisher and License: THB. Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source.

Abstract

**Background:** Iron deficiency is the most common cause of anemia, especially in reproductive-aged women. If not treated, it leads to weakness, fatigue, menorrhagia, amenorrhea in females and can cause serious consequences such as heart problems and complications in pregnant ladies such as premature births and low birth weight babies. Thus, it is necessary to prescribe iron supplementation in iron-deficient women to avoid complications in the later stage.

**Objective:** The objective of this study was to evaluate the efficacy of the combination of ferric pyrophosphate and folic acid in reproductive-aged women who suffered from iron deficiency.

**Methods:** Electronic medical records of 100 reproductive-aged women deficient in iron were analyzed. The baseline hemoglobin and iron parameters were noted. They were prescribed a 30 mg tablet combination of ferric pyrophosphate and folic acid, and the parameters were noted at 4 weeks, 8 weeks, and 12 weeks. The data was statistically analyzed by SPSS version 26.0.

**Results:** The hemoglobin (hemoglobin, total erythrocytes, mean corpuscular volume, red cell distribution width, haematocrit) and iron parameters (serum iron, ferritin, transferrin saturation, serum transferrin) showed significant improvement in week 4, which continued till week 12. The RDW levels showed much improvement after week 4 till week 12.

**Conclusion:** Our study concluded that the combination of ferric pyrophosphate and folic acid in tablet form significantly improves the hemoglobin and iron parameters within 4 weeks and showed further improvement until 12 weeks without any complaint of side effects.

**Keywords:** Iron pyrophosphate; Folic acid; Iron deficiency; Anemia; Hemoglobin
Introduction

Over the world, iron deficiency and iron deficiency anaemia have caused an immense disease burden. In 2016, there were over 1·2 billion cases of IDA globally. In low-income and middle-income countries (LMICs), IDA is globally among the five major causes of years lived with disability and is the leading cause of years lived with disability among women across 35 countries[1]. Controlling anaemia has become a global health priority: WHO is aiming for a 50% reduction in anaemia prevalence in women by 2025[2].

When iron intake is insufficient to meet physiological or pathological losses requirements, body iron stores become depleted. An absolute iron deficiency arises when iron stores are inadequate to meet the person's needs and is especially common in young children (younger than five years) and premenopausal (especially pregnant) women. In inflammation patients, withholding iron from the plasma promotes iron-deficient erythropoiesis and anaemia despite adequate body iron stores (functional iron deficiency). This process is common in patients with complex medical or surgical disorders, in people living in areas where infection prevalence is high, and in patients receiving erythropoiesis-stimulating agents[3]. Iron deficiency anemia is defined as hemoglobin less <110 g/L and at least one additional laboratory indicator such as haemoglobin concentration, mean cell volume, serum ferritin, erythrocyte protoporphyrin concentrations of iron deficiency[4]. Iron is crucial for numerous physiological and cellular processes, and iron deficiency causes diverse health consequences.

Managing iron deficiency is a significant and complex challenge faced by practitioners of medicine, nutrition, and public health worldwide. Practitioners prescribe various iron supplements in tablets or syrups to compensate for iron deficiency. The available oral iron salts include ferrous sulfate, ferrous fumarate, and ferric citrate[5]. Ferrous sulfate is the most frequently prescribed iron salt to prevent and treat iron deficiency anemia in pregnancy[6,7]. The adverse effects of conventional iron salts cannot be ignored, including dyspepsia, diarrhea, nausea, vomiting, abdominal pain, constipation, and blackish discoloration of stools. Phytates, calcium, and tannins hinder the absorption of conventional iron salts in the food by changing absorbable ferrous form to a comparatively less absorbable ferric form through an oxidation reaction[8]. To conquer these shortcomings, newer iron salts such as ferric pyrophosphate, ferrous ascorbate, and iron polymaltose complex were introduced, of which ferric pyrophosphate is the recent one showing promising results in clinical studies[9].

A common generic approach for iron deficiency in adults consists of 150-200 mg of elemental iron daily. This approach entails prescribing one ferrous sulfate tablet three times daily since each tablet contains approximately 60 mg of elemental iron. Assuming that 10% of the iron is absorbed, the hemoglobin concentration may entirely correct after four weeks in patients having moderate, uncomplicated iron deficiency (about 500-800 mg of iron, enough for 500 to 800 mL of packed red blood cells, or sufficient to raise the whole blood hemoglobin 2-3 g/dL)[10]. To further
replenish iron stores, some recommend continuing this regimen for several additional months\[^{[11]}\]. Unfortunately, this approach often fails as up to 20 percent of patients experience gastrointestinal discomfort while taking 180 mg of elemental iron per day using this regimen, and 30% of some patient groups may self-discontinue the medication\[^{[12,13]}\].

Major stumbling blocks toward successful oral iron therapy are dose-related, upper gastrointestinal side effects such as nausea and epigastric discomfort, which occur approximately one hour after ingestion. If a patient quickly becomes constipated or nauseated from a commonly recommended dose of 150-200 mg of daily elemental iron, dose reductions are applied. Changes in iron salts (and hence elemental iron per tablet) and formulations are commonly tried, and most involve dose reductions by lengthening the dose interval\[^{[14]}\].

In cases where the prevalence of iron deficiency is high in anemic females, folic acid is given in combination with 400 µg of iron. Folic acid is significant for erythropoiesis in the body and important for the synthesis & repair of DNA & other genetic material, and it is crucial for cell division. In pregnant women, it helps prevent neural tube irregularities, such as spina bifida and anencephaly in the fetus\[^{[15]}\]. In our study, we prescribed a tablet comprising a combination of ferric pyrophosphate (elemental iron 30 mg) and folic acid (200 mcg) in tablet form. Our study aimed to assess the efficacy of this combination in the management of iron deficiency in women.

Materials and Methods

We carried out a retrospective study on 100 women of reproductive age who visited from January 2019 to June 2020 with chief complaints of menorrhagia, weakness, or amenorrhea. They were prescribed a tablet comprising a combination of ferric pyrophosphate (elemental iron 30 mg) and folic acid (200 mcg) as they were iron deficient. No other drugs were prescribed. The inclusion criteria comprised females aged 18-50 years and who took the combination as prescribed. The exclusion criteria included females under 18 and more than 50 years of age. Also, those females taking any other medications apart from the prescribed combination were excluded.

The hemoglobin (hemoglobin, total erythrocytes, haematocrit, mean corpuscular volume (MCV) and Red Cell Distribution Width (RDW) and iron parameters (plasma iron, plasma transferrin, plasma transferrin saturation, plasma ferritin) were assessed at baseline, 4 weeks, 8 weeks, and 12 weeks. Statistical analysis was performed using SPSS version 26.0.

Results

The mean age of the women was 34.35 ± 9.05 years, and BMI was 27.25 ± 3.48 kg/m2. The hemoglobin and iron status parameters at baseline, 4 weeks, 8 weeks, and 12 weeks are shown in table 1. The hemoglobin and iron
parameters showed a significant improvement from baseline till the 12th week of the treatment period in all individuals. The mean difference in hemoglobin levels, serum iron levels, ferritin, transferrin saturation, total erythrocytes, haematocrit, MCV, RDW, and serum transferrin at baseline, 4 weeks, 8 weeks, and 12 weeks is shown in figure 1-9 respectively. The mean RDW levels showed much improvement after 4 weeks.

Figure 1: Mean difference in hemoglobin levels at baseline, 4 weeks, 8 weeks, and 12 weeks

Figure 2: Mean difference in serum iron levels at baseline, 4 weeks, 8 weeks, and 12 weeks
Figure 3: Mean difference in ferritin levels at baseline, 4 weeks, 8 weeks, and 12 weeks

Figure 4: Mean difference in transferrin saturation levels at baseline, 4 weeks, 8 weeks, and 12 weeks
Figure 5: Mean difference in total erythrocytes levels at baseline, 4 weeks, 8 weeks, and 12 weeks

Figure 6: Mean difference in haematocrit levels at baseline, 4 weeks, 8 weeks, and 12 weeks
**Figure 7:** Mean difference in MCV levels at baseline, 4 weeks, 8 weeks, and 12 weeks

**Figure 8:** Mean difference in RDW levels at baseline, 4 weeks, 8 weeks, and 12 weeks
Figure 9: Mean difference in serum transferrin levels at baseline, 4 weeks, 8 weeks, and 12 weeks

Table 1: Mean difference of hemoglobin and iron parameters at baseline, 4 weeks, 8 weeks, and 12 weeks

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (Hb) (g/dl)</td>
<td>8.94 ± 1.19</td>
<td>10.87 ± 1.13</td>
<td>11.13 ± 0.37</td>
<td>12.63 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Iron (mcg/dl)</td>
<td>7.66 ± 1.55</td>
<td>19.67 ± 2.51</td>
<td>23.83 ± 2.16</td>
<td>33.08 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin (mcg/l)</td>
<td>24.17 ± 1.94</td>
<td>44.03 ± 5.49</td>
<td>47.74 ± 4.7</td>
<td>95.21 ± 16.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin Saturation(%)</td>
<td>13.76 ± 1.44</td>
<td>23.86 ± 4.61</td>
<td>27.14 ± 3.2</td>
<td>37.38 ± 1.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Erythrocytes (million/mm³)</td>
<td>3.61 ± 0.54</td>
<td>4.34 ± 0.57</td>
<td>4.98 ± 0.11</td>
<td>5.31 ± 0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>25.72 ± 2.62</td>
<td>31.14 ± 2.34</td>
<td>33.97 ± 0.17</td>
<td>37.74 ± 1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCV(µm³)</td>
<td>65.76 ± 3.15</td>
<td>68.85 ± 3.07</td>
<td>75.02 ± 0.14</td>
<td>82.80 ± 6.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.59 ± 10.20</td>
<td>13.00 ± 1.00</td>
<td>14.41 ± 0.51</td>
<td>15.00 ± 0.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Transferrin</td>
<td>479.34 ± 28.69</td>
<td>429.84 ± 27.38</td>
<td>355.4 ± 9.15</td>
<td>289.5 ± 17.73</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
To detect differences in treatments across multiple follow-ups, Friedman test was used. The difference between mean hemoglobin levels, total erythrocytes, haematocrit, MCV, and RDW at baseline till 12 weeks was found to be highly statistically significant. The mean difference of serum iron levels, ferritin levels, transferrin saturation levels, and serum transferrin levels at baseline till 12 weeks was found to be highly statistically significant as well.

Discussion
As per Zariwala et al., the modified-released formulations containing ferrous sulphate plus ascorbic acid (Ferrograd C) and ferrous gluconate plus minerals and vitamins (Feroglobin B12) demonstrated low iron absorption. Syrup preparations containing ferrous gluconate plus folic acid (Feroglobin B12) and ferrous gluconate plus ascorbic acid (Floradix) demonstrated relatively low iron absorption. Conventional-release ferrous sulphate, therefore, demonstrated the overall highest rate of iron uptake, whereas the lowest level of iron uptake was from ferrous sulphate plus ascorbic acid (Ferrograd C) modified-release tablets\[16\].

Given the documentation of iron deficiency in women and low iron absorption levels with other iron formulations, we aimed to evaluate the efficacy of the combination of iron pyrophosphate and folic acid in iron-deficient reproductive-aged women. Since this was a retrospective study, electronic medical records (EMR) of 100 women were assessed who was found to be iron deficient. These women were prescribed 30 mg tablet, which comprised a combination of iron pyrophosphate and folic acid. No other drugs were prescribed apart from this combination. Baseline readings were noted which comprised of hemoglobin and iron parameters. Follow-up was taken after 4 weeks followed by 8th and 12th weeks. The present study clearly shows that taking this combination helped significantly improve hemoglobin and iron parameters over four weeks, which showed further improvement until 12 weeks. The hemoglobin and iron parameters difference levels were found to be highly statistically significant. None of the women complained of any side effects after taking the tablet.

Not many studies are available that have studied the efficacy of the combination of iron pyrophosphate with folic acid in the management of iron deficiency. Craven et al., investigated the micronized dispersible form of ferric pyrophosphate (MDFP) absorption kinetics with an emulsifier coating and folic acid in a powdered multivitamin supplement versus ferrous fumarate (non-encapsulated) in a traditional tablet supplement in healthy pregnant women. Both folic acid and iron were absorbed from the powdered supplement. However, the area under the curve and doses, based on the differences, the relative bioavailability of iron was higher from the tablet supplement than the powdered supplement (0.22), while folic acid was greater (1.8)\[17\].
Parker et al. carried out a survey in which they found that oral ferric pyrophosphate formulation therapy can serve as the potent choice of treatment for iron deficiency in pregnancy, both therapeutically and prophylactically. There was
a rise in Hb from baseline to week 8, which was 2.01 g/dl. Adverse events were reported in only 10 patients (<0.09%), none requiring discontinuation of therapy[18].

Considering the burden of iron deficiency not only in pregnant women but also in non-pregnant women, it is crucial to assess women at risk for iron deficiency by analysis of plasma ferritin prior to or in early pregnancy[19]. Timely action will help overcome the burden of iron deficiency and will also be helpful in women who are planning a pregnancy in the future.

Conclusion
The present study concludes that iron supplementation in combination with folic acid can help in significant improvement of hemoglobin and iron parameters within 4 weeks and can improve the levels further with time. Thus, assessing the iron deficiency timely can help cope with the iron deficiency management and lessen the burden of iron deficiency.

Ethical Approval: N/A
Conflict of Interest: None
Financial Disclosure: Nil

Reference