Original Research Article

# A Comparative Study Of Efficacy And Safety Of Iron Polymaltose Complex Versus Ferrous Sulphate In Female Patients with Iron deficiency

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## Abstract

**Introduction:** According to the WHO, iron deficiency is the most common form of malnutrition in the world. In India, 45% adult females have iron deficiency. Ferrous Sulphate (FS), a bivalent iron salt remains the established and the standard treatment of iron deficiency. Iron polymaltose complex (IPC) causes less or no gastric irritation and eliminates the need for frequent dosing thereby improving patient compliance. The purpose of the study was to compare the efficacy and safety profiles of iron polymaltose complex and ferrous sulphate in female patients with iron deficiency anemia. **Methods:** 150 patients of iron deficiency anemia were enrolled in the study with 75 patients each in two groups. One group received iron polymaltose complex and the other group received ferrous sulphate for a period of 12 weeks. Response was assessed by measuring hemoglobin level, serum iron level, serum ferritin and total iron binding. The results within the groups were analyzed using paired student't' test and between the groups using unpaired student't' test. P value < 0.05 was considered statistically significant. **Results:** Both iron polymaltose complex and ferrous sulphate significantly improved hemoglobin level, serum iron level, total iron binding capacity. The efficacy achieved with both these drugs was comparable, but overall adverse effects were more common in the FS group compared to the IPC group. **Conclusion:** Iron polymaltose complex can be considered as a useful alternative formulation over ferrous sulphate as it had fewer adverse effects.

**Keywords:** Iron Deficiency Anemia, Iron Polymaltose Complex, Ferrous Sulphate.



## Introduction

According to the WHO, iron deficiency is the most common form of malnutrition in the world, affecting around 2 billion people worldwide, which corresponds to 25% of population globally[1]. Absolute iron deficiency constitutes a major source of morbidity throughout the world. The consequences of anemia for women include increased risk of low birth weight or prematurity, perinatal and neonatal mortality, inadequate iron stores for the newborn, increased risk of maternal morbidity and mortality, and lowered physical activity, mental concentration, and productivity[2].

Iron Deficiency Anemia (IDA) responds promptly to oral iron therapy. Various iron preparations with different elemental iron content are available in the market. Iron salts can cause nausea, vomiting, abdominal cramps, constipation and diarrhoea. This often results in poor compliance with therapy. Although administration with food improves tolerability, it decreases iron bioavailability. Another important drawback is their potential toxicity in case of overdosage[3].

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Ferrous Sulphate (FS), remains the established and the standard treatment of iron deficiency given its acceptable tolerability, high effectiveness, and low cost[4]. However, the use of this is limited by low and variable absorption, chelation by food products, and free radical-mediated mucosal luminal damage[11,12]. Iron polymaltose complex (IPC) containing elemental iron in a nonionic state, causes less or no gastric irritation and eliminates the need for frequent dosing thereby improving patient compliance[7]. The rationale for development was to produce a compound with good bioavailability across a wide range of conditions, with no troublesome interactions with food or other medications and with excellent tolerability and long-term safety[3]. The purpose of the study was to compare the efficacy and safety profiles of iron polymaltose complex and ferrous sulphate in iron deficiency anemia in female patients.

## Materials and methods

A prospective comparative study was conducted in our institute from August 2018 to January 2019. A total of 150 female patients with iron deficiency anaemia were included in the study.

**Inclusion criteria**

1. Female patients in the age group of 18 to 60 years
2. Patients having microcytic hypochromic anemia due to iron deficiency
3. Patients with hemoglobin less than 10g/dl

**Exclusion criteria**

1. Anemia due to acute haemorrhage
2. Patients who have undergone resective gastric and small intestinal surgery
3. Patients having anemia due to bleeding disorders

4. Known cases of hepatic and renal failure

**Data collection**

A proforma containing detailed information about each patient was prepared according to the protocol designed for the study, which consists of demographic details, relevant history, general examination, physical examination with special emphasis on signs of IDA. Written and informed consent was obtained from all patients in local language prior to screening and enrollment. Clearance was taken from the Ethical committee.

Laboratory investigations at the baseline included hemoglobin level, peripheral blood picture, Serum iron level, Serum ferritin and Total iron binding capacity (TIBC).

Out of 150 patients, 75 patients were assigned to the FS group and IPC group each randomly. Patients in one group received IPC (100 mg elemental iron) one tablet orally once daily, and the other group received FS (60 mg elemental iron) one tablet orally twice daily, for a period of 12 weeks. Response to treatment was assessed by measuring hemoglobin level, serum iron level, serum ferritin and total iron binding capacity at 4weeks, 8weeks and 12 weeks.

Composite score of physical wellbeing (table1) and adverse effects (Table 2) occurred during the treatment are also recorded.

**Table 1: Scoring and grading of symptoms**

| Score | Grade | Description |
|---|---|---|
| 0 | Nil | No occurrence of symptoms |
| 1 | Mild | Symptom present but not troublesome |
| 2 | Moderate | Annoying and slightly disturbing daily activities |
| 3 | Severe | Continuously present, interferes with daily activities |

Minimum score = 0 Maximum score = 24

**Table 2:Severity of adverse effects**

| Mild | Discomfort but tolerable |
|---|---|
| Moderate | Discomfort and required treatment |
| Severe | Required stopping iron supplement |

The eight symptoms Fatigue, Malaise, Loss of appetite, Breathlessness, Palpitations, Giddiness, Irritability and reduced work performance were scored at 0,4,8 and 12 weeks. Each symptom has a score ranging from 0 to 3. The composite score of physical well being was calculated by scoring these symptoms. The sum of the scores was recorded with minimum score being 0 and maximum score being 24.

**Statistical analysis**

The demographic data was analyzed using descriptive statistics. The results like change in hemoglobin levels, serum iron levels, total iron binding capacity and serum ferritin within the groups were analyzed using paired student't' test and between the groups using unpaired student't' test. P value < 0.05 was considered statistically significant. The composite scores of physical well being within the group and between the groups were analyzed using Wilcoxon sign rank test and Mann Whitney U test respectively (p value <0.001).

**Results**

Data of all 150 patients were analyzed to assess efficacy and safety of both the drugs individually and in comparison with each other. Demographic data and other baseline characteristics of all subjects are shown in Table 3.

**Table 3: Demographic and baseline characteristics of both the groups**

| S. No | Parameter | Iron polymaltose complex | Ferrous sulphate |
|---|---|---|---|
| 1 | No. of patients | 75 | 75 |
| 2 | Age, yrs (mean ± SD) | 33.39±10.62 | 32.93±12.65 |
| 3 | Hemoglobin (g/dL) (mean ± SD) | 7.24±1.11 | 7.10±1.25 |
| 4 | Serum iron (mcg/dL, mean ± SD) | 45.88±9.33 | 45.74±10.60 |
| 5 | Serum ferritin (ng/mL, mean ±SD) | 11.20±1.83 | 11.08±0.94 |
| 6 | Total iron binding capacity (mcg/dL, mean ± SD) | 477.89±24.85 | 475.78±28.78 |
| 7 | Composite score of physical well being (mean ±SD) | 3.57±1.63 | 4.01±2.14 |

The demographic data and other characteristics, composite score of physical well being of the patients were comparable in both the groups at the baseline.

**Efficacy analysis – iron polymaltose group**

The effect of IPC on hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW from baseline, 4 weeks, 8 weeks, 12 weeks were compared using paired t test and the results were shown in the table 4.

**Table 4: Comparison of hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW from baseline, 4 weeks, 8 weeks, 12 weeks within iron polymaltose group using paired t test**

| Parameter | | 0 week | 4th week | 8th week | 12th week |
|---|---|---|---|---|---|
| Hb | Mean | 7.24 | 8.40 | 9.44 | 10.24 |
| | S.D | 1.11 | 0.89 | 0.89 | 0.80 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| Serum Iron | Mean | 45.88 | 63.24 | 71.80 | 78.94 |
| | S.D | 9.33 | 8.30 | 8.46 | 8.71 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| Serum Ferritin | Mean | 11.20 | 13.01 | 14.68 | 16.80 |
| | S.D | 1.83 | 1.70 | 1.83 | 2.49 |
| | P value | 0.001 | | 0.001 | |

| | | | | | |
|---|---|---|---|---|---|
| | | | 0.001 | | |
| **TIBC** | Mean | 477.89 | 432.56 | 420.05 | 404.13 |
| | S.D | 24.85 | 19.00 | 18.66 | 17.24 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| **CSPW** | Mean | 3.57 | 2.04 | 1.06 | 0.41 |
| | S.D | 1.63 | 1.16 | 0.82 | 0.57 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |

Mean hemoglobin levels & serum iron levels, were significantly higher at 4th, 8th and 12th week compared to baseline value and the mean rise in hemoglobin level & serum iron levels was significantly higher during first 4 weeks compared to other observed time periods.

Mean total iron binding capacity levels & composite scores of physical well being were significantly lower at 4th, 8th and 12th weeks compared to baseline value, and the mean reduction in total iron binding capacity level & composite score of physical well being was significantly higher during first 4 weeks compared to other observed time periods.

**Efficacy analysis – ferrous sulphate group**

The effect of FS on hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW from baseline, 4 weeks, weeks, 12 weeks were compared using paired t test and the results were shown in the table 5.

**Table 5: Comparison of hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW from baseline, 4 weeks, 8 weeks, 12 weeks within Ferrous Sulphate group using paired t test.**

| Parameter | | 0 week | 4th week | 8th week | 12th week |
|---|---|---|---|---|---|
| **Hb** | Mean | 7.10 | 8.70 | 9.63 | 10.37 |
| | S.D | 1.25 | 0.86 | 0.81 | 0.89 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| **Serum Iron** | Mean | 45.74 | 64.14 | 72.02 | 79.28 |
| | S.D | 10.60 | 10.20 | 8.08 | 6.63 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| **Serum Ferritin** | Mean | 11.08 | 13.84 | 15.11 | 17.10 |
| | S.D | 0.94 | 1.48 | 2.18 | 3.64 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| **TIBC** | Mean | 475.78 | 430.57 | 418.33 | 400.93 |
| | S.D | 28.78 | 20.44 | 18.29 | 16.76 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |
| **CSPW** | Mean | 4.01 | 2.50 | 1.25 | 0.14 |
| | S.D | 2.14 | 1.57 | 1.09 | 0.48 |
| | P value | 0.001 | | 0.001 | |
| | | | 0.001 | | |

Mean hemoglobin levels & serum iron levels, were significantly higher at 4th, 8th and 12th weeks compared to baseline value, And The mean rise in hemoglobin level & serum iron levels was significantly higher during first 4 weeks compared to other observed time periods.

Mean total iron binding capacity levels & composite scores of physical well being were significantly lower at 4th, 8th and 12th weeks compared to baseline value, and The mean reduction in total iron binding capacity level & composite score of physical well being was significantly higher during first 4 weeks compared to other observed time periods.

**Comparision of efficacy between iron polymaltose and ferrous sulphate groups**

The effect of iron polymaltose complex and ferrous sulphate on hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW at baseline, 4 weeks, 8 weeks and 12 weeks were compared using unpaired t test and results were shown in the table 6.

**Table 6: Comparision of hemoglobin levels, serum iron, serum ferritin, TIBC & CSPW at baseline, 4 weeks, 8 weeks and 12 weeks in between iron polymaltose and ferrous sulphate groups using unpaired t test**

| Parameter | | 0 week | 4th week | 8th week | 12th week |
|---|---|---|---|---|---|
| **Mean Hb** | IPC | 7.24 | 8.40 | 9.44 | 10.24 |
| | FS | 7.10 | 8.70 | 9.63 | 10.37 |
| | P Value | 0.476 | 0.036 | 0.162 | 0.339 |
| **Mean Serum Iron** | IPC | 45.88 | 63.24 | 71.80 | 78.94 |
| | FS | 45.74 | 64.14 | 72.02 | 79.28 |
| | P Value | 0.432 | 0.007 | 0.247 | 0.192 |
| **Mean Serum Ferritin** | IPC | 11.20 | 13.01 | 14.68 | 16.80 |
| | FS | 11.08 | 13.84 | 15.11 | 17.10 |
| | P Value | 0.477 | 0.008 | 0.138 | 0.180 |
| **Mean TIBC** | IPC | 477.89 | 432.56 | 420.05 | 404.13 |

| | | | | | |
|---|---|---|---|---|---|
| | FS | 475.78 | 430.57 | 418.33 | 400.93 |
| | P Value | 0.090 | 0.146 | 0.223 | 0.075 |
| **Mean CSPW** | IPC | 3.57 | 2.04 | 1.06 | 0.41 |
| | FS | 4.01 | 2.50 | 1.25 | 0.14 |
| | P Value | 0.16 | 0.04 | 0.24 | 0.002 |

**Table 7: Adverse effects of both iron polymaltose complex and ferrous sulphate groups**

| Adverse effects | IPC group | FS group |
|---|---|---|
| Total number of patients having adverse effects | 14(18.6%) | 37(49.3%) |
| GI intolerance (nausea,vomiting,heartburn) | 12(16%) | 32(42.6%) |
| Constipation | 6(8%) | 16(21.3%) |
| Metallic taste | 2(2.6%) | 8(10.6%) |
| Diarrhoea | 0 | 2(2.6%) |
| Rashes | 0 | 1(1.3%) |

**Safety analysis**

The total number of patients having adverse effects was 14 and 37 in IPC and FS groups respectively. GI intolerance and constipation were commonly observed in both the groups. The adverse effects in both groups were tolerable and none of the patients needed any intervention or had to discontinue the study drugs. From the above table it was clear that adverse effects were more common in the FS group than in the IPC group.

**Discussion**

Iron deficiency anaemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. Prevalence of anemia in South Asia is among the highest in the world, mirroring overall high rates of malnutrition. In India 30% adult males, 45% adult females, 80% pregnant females and 60% children suffer from iron deficiency anemia[8]. The present study is limited to women only as they are more prone to the chronic, debilitating iron deficiency anaemia. The present study was conducted in all women irrespective of their pregnancy status keeping the factor that screening of pregnant women was improved and non pregnant women were at increased risk of getting iron deficiency anaemia as there was no such screening mandatory for them.

Bentley and PL Griffiths confirmed that rural women would have a higher prevalence of anemia compared with urban women, particularly among the lower income groups[2]. The literature reported few similar Indian studies [9,10] but unlike present study they were confined to urban areas.

Oral iron supplementation is the standard treatment for patients with iron deficiency[4]. Ferrous Sulphate, a bivalent iron salt remains the established and the standard treatment of iron deficiency given its acceptable tolerability, high effectiveness, and low cost[4]. Iron polymaltose complex containing elemental iron in a nonionic state, causes less or no gastric irritation and eliminates the need for frequent dosing thereby improving patient compliance[7]. There is an ongoing debate over the efficacy of IPC in the background of pressure marketing done by the manufacturers and lack of data in the Indian context. The present study was thus designed to compare the efficacy and side-effects of iron polymaltose complex versus the conventional ferrous sulphate preparations in treatment of iron deficiency anemia.

For estimating efficacy of both preparations, laboratory parameters such as hemoglobin concentration, serum iron, serum ferritin and total iron binding capacity values were chosen, because they are commonly preferred by clinicians in their clinical practice and gives better idea for diagnosis, prognosis and also evaluation of the therapy. Measurement of hemoglobin or hematocrit is the most cost efficient and commonly used method to screen for anemia. Determining the concentration of hemoglobin, an iron-containing protein, in red blood cells is a more sensitive and direct indicator of anemia than hematocrit (percentage of red blood cells in whole blood)[11]. The present study has taken hemoglobin concentration as primary efficacy parameter because of its importance.

Serum ferritin was not included in some previous studies may be because they were conducted in pregnant women[9,10]. In pregnancy serum ferritin levels decline even in women ingesting daily supplements of iron[12]. The most accurate initial diagnostic test for IDA is the serum ferritin measurement[13]. This correlates with total body iron stores. However, ferritin levels can be raised if infection or inflammation is present, even if iron stores are low. When serum ferritin is reported as normal or high, additional tests like serum iron and total iron binding capacity will be considered if iron deficiency is suspected clinically[14]. More sophisticated tests (e.g. serum free transferrin receptor and others), that are unaffected by concurrent diseases are being investigated but not yet available in most diagnostic facilities[14].

Results from this large, randomized study show that improvement in iron status indicators was comparable with iron polymaltose complex and ferrous sulphate over a 12 week period in females with iron deficiency anaemia. A number of studies have previously demonstrated that equal amount of iron is available from ferrous sulphate or iron polymaltose complex in correcting hemoglobin levels over a twelve weeks observation period[15,16]. The present study supported their conclusion that there was no difference whichever drug is given. The comparison of two drugs in some studies suggest Iron polymaltose complex being as effective or even superior to ferrous sulphates[9,10]. But some studies contradict these results[17,18].

The efficacy and improvement in iron status indicators (hemoglobin, serum iron, serum ferritin and total iron binding capacity) were comparable in both groups. In a similar study, Irfan Ullah Marwat et al [19] showed significant increase in hemoglobin levels with both IPC and FS preparations. In another study, Sozmen et al [20] showed both preparations induced comparable rise of hemoglobin and serum iron levels. Few other studies showed that there was no difference observed between the two groups[9,19].

Bopche et al, [10] showed that that FS group had significant increase in Hb level from baseline to final follow-up. Their results were same as those reported by Arvas and Langstaff [21,22]. In several other studies, the response to IPC was not adequate. [18] However, Reddy PSN et al [23] and Badhwar et al [24] showed superiority of IPC preparations over ferrous sulphates.

There was no significant difference in composite score of physical wellbeing between the two groups at 4, 8 and 12 week time periods. This suggests that the extent of improvement in symptoms was similar in both the groups in accordance with the recovery of iron status. This may be due to rapid diminution of symptoms seen with iron therapy that occurs even before the actual improvement in iron status is evident.

Coming to the adverse effects, they were more common in the FS group than in the IPC group in the present study. About 49.3% of the patients in FS group reported adverse effects where as in IPC group the incidence reported was only 18.6%. Similar observations were seen in the Indian populations studied by Reddy PSN et al, [23] and Rajyadhyaksha et al [25]. A drawback of oral iron supplementation, particularly ferrous sulfate, is the high incidence of gastrointestinal

adverse events such as nausea, vomiting, abdominal cramps, constipation and diarrhea, and tooth staining[26]. Randomized studies in adults have confirmed a lower rate of gastrointestinal symptoms with IPC versus ferrous sulfate [15,21]. The differences in safety profiles between the two preparations are attributed to a slower release of iron from the stable IPC complex[27]. Rapid iron release from ferrous sulfate within the gastric lumen can overload the active, control uptake mechanism in the enterocytes, leading to local gut reactions and symptoms such as vomiting and dyspepsia. Overload of the active uptake mechanism also leads to passive absorption via the intercellular route and absorption of iron from the gut directly into the bloodstream, with a consequent increase in nontransferrin bound iron (NTBI). NTBI iron is known to induce oxidative stress that can cause systemic adverse events including nausea. The rise in NTBI thus is negligible after IPC dosing since the size of the hydroxide complex means that there is almost no passive diffusion and the slow release of iron avoids overload of the active transport mechanism, [27] but when iron is given in the form of ferrous salts, rapid release of iron means that there is a dose-dependent passive absorption of iron. As a consequence, ferrous sulfate is associated with increased levels of NTBI and increased oxidative stress, whereas IPC administration is not[28].

Taking ferrous salts at mealtimes improves gastrointestinal tolerance, but markedly reduces iron bioavailability such that it is recommended to take ferrous sulfate between meals. IPC, in contrast, can be taken at meal times without compromising bioavailability or effectiveness. The good tolerability of IPC was confirmed in a randomized trial of IPC versus ferrous gluconate in a series of 105 healthy infants to assess their efficacy in the prevention of anemia. Adverse effects such as vomiting, diarrhea, constipation, and discolored teeth were significantly less frequent in the IPC treatment group, although mean Hb levels were higher in the ferrous gluconate arm[29].

In the present study, no patient discontinued treatment due to adverse effects. Patient compliance was acceptable with both preparations. However, in several clinical trials, early discontinuation of treatment due to adverse effects was lower with IPC than with ferrous iron preparations. It therefore appears that patient compliance may be better with IPC than with classic ferrous sulphate preparations[3].

IPC is generally well tolerated and appears to cause significantly less gastrointestinal disturbance than ferrous salts. Both the incidence and severity of adverse events in most clinical trials has been lower with IPC than with ferrous sulphate. IPC is also safer in cases of accidental overdose, and no fatalities have been reported. Recent studies suggest that ferrous sulphate may be associated with oxidative stress reactions, but there are indications that this concern does not apply to IPC[3].

As with all studies the present study also possesses few limitations. The normal rise in the hemoglobin level usually starts after three days of the starting of iron therapy, and the rate in rise of the hemoglobin level in pregnant women is 0.8 g/dl per week as compared to non-pregnant women of 1.0-1.2 g/dl per week[30]. Although not up to the expectation, the rate of increase in the hemoglobin concentration was found to be significant in this study. The reason for fewer rises in the hemoglobin level is unidentified, as the dose of iron was sufficient according to requirement. However if the losses (for example bleeding) exceed the amount of iron absorbed daily, the hemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states. The presence of underlying inflammation may also lead to a poor response to therapy.

The study was one of the few research programs done in India comparing the efficacy and safety of two oral iron preparations, IPC and FS. However further research has to be done to correlate the findings of the present study before implementing them in therapeutic guidelines.

**Conclusion**

- The present study has shown that both iron polymaltose complex and ferrous sulphate are effective in improving the iron status and symptoms of patients with iron deficiency anemia.
- The mean rise/reduction in various iron status indicators was significantly higher during first 4 weeks compared to other observed time periods(8 and 12weeks) with respect to both Iron polymaltose compex and ferrous sulphate.
- IPC is generally well tolerated and appears to cause significantly less gastrointestinal disturbance than ferrous salts.
- Taking into consideration the definition of therapeutic equivalency, which states that two preparations are equivalent if they demonstrate the same efficacy and safety, it can be concluded that IPC is superior to iron salts, due to the fact of that it displays equal efficacy, but has a superior safety profile.

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