



Original Research Article

A Comparative Study of the Efficacy and Tolerability of Carbonyl Iron and Ferrous Sulfate in Iron Deficiency Anaemia

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ABSTRACT

The prospective randomized comparative study was performed to find out the efficacy & tolerability of carbonyl iron over ferrous sulfate from August 2006 to July 2007. The study was conducted at Government Medical College, Miraj. In this study we included 50 adult patients of either sex with iron deficiency anemia visiting Medicine outpatient department. Adult male / female patients with mild to moderate Iron deficiency anaemia (Hb. 8 to 11gm %) were included in the study. They were divided into two equal groups for comparison. The mean rise of haemoglobin level was more with ferrous sulphate at the time of all follow ups. Adverse effects were seen more in number and intensity with ferrous sulphate. Individual efficacy of both compounds was good but carbonyl iron was better tolerated.

Key Words: Iron deficiency anemia, hemoglobin, carbonyl iron, ferrous sulfate

INTRODUCTION

Iron is not like gold that glitters or silver that shines; however it outshines both in its biological importance. Iron deficiency is an insidious problem, unnoticed; often not diagnosed, yet it saps the vitality of the nation.

Iron deficiency is probably the most common nutritional deficiency disorder in the world. A recent estimate based on WHO criteria indicated that around 600-700 million people worldwide have marked iron deficiency anaemia (IDA) and bulk of these people live in developing countries like India. In developed countries, the prevalence of iron deficiency anaemia is much lower and usually varies between 2% and 8%. [1]

In developing countries, up to 20% to 40% of infants and pregnant women may be affected. It results from an inadequate dietary intake of iron, inadequate iron absorption or blood loss. [2]

Iron deficiency anaemia is widely prevalent in India affecting 20% adult males, 40% children and adult non-pregnant females, and 80% of pregnant females. [3]

Iron preparations like Ferrous Sulfate (FS), Iron Polymaltose Complex (IPC) and Carbonyl Iron are extensively prescribed for the prevention and treatment of Iron deficiency anaemia. Orally administered Ferrous Sulfate, the least expensive among these preparations, is the treatment of choice for Iron deficiency anaemia. [4]

Iron Polysaccharide (Polymaltose) complex, a compound of Ferrihydrate and carbohydrate and Carbonyl Iron, a small particle preparation of highly purified metallic iron are widely prescribed for Iron deficiency anaemia. [5]

Though widely prescribed, none of the iron preparations viz Carbonyl Iron, Iron Polymaltose Complex and Ferrous Sulfate have been adequately studied in the Indian setting, either individually or in comparison. Hence there is a need to compare the efficacy of these iron preparations. It is also necessary to compare their tolerability because this influences patient compliance and hence therapeutic outcome.

In the present study, Carbonyl Iron, whose bioavailability has been questioned will be compared with Ferrous Sulfate, the most commonly prescribed and the least expensive preparation having good efficacy

SUBJECTS AND METHODS

The study was carried out in adult patients of either sex visiting Medicine outpatient department (OPD) at Govt. Medical College Hospital, Miraj and P.V.P. General Hospital, Sangli.

This was a prospective, randomized, observer blind and comparative clinical trial. 50 patients of mild to moderate iron deficiency anaemia (Hb. 8–11 gm%) were enrolled in the study as per selection criteria after obtaining written informed consent.

Patients were randomized into two groups (25 patients in each group). Patients received following drug therapy after deworming with Albendazole 400 mg, if necessary.

Group A: Patients received Carbonyl Iron 100 mg once daily.

Group B: Patients received Ferrous Sulfate 200 mg three times a day.

The drug therapy in all the three groups was given for 12 weeks. Patients

were asked to avoid tea, coffee, phytates and tannin.

The following laboratory investigations were carried out:-

1. Haemogram including Hb. by Cyanmethemoglobin method.
2. Peripheral smear (P.S.)
3. Erythrocyte sedimentation rate (E.S.R.).
4. Stool examination.

These investigations were done on O day, 2nd week, 4th week, 8th week and 12th week of enrolment. The patients were followed up on 2nd week, 4th week, 8th week and 12th week and as and when required.

At each follow visit, patients were examined for signs and symptoms of iron deficiency anaemia. All patients were also subjected to detail general and systemic examination at each visit. Compliance was checked by verbal enquiry. Verification was done by asking them to bring the used packets of the drugs.

Safety variables: History of vomiting after the dosage and colour of the stools were enquired about. Any drug induced side effects as experienced by patient during the course of treatment with the study drugs were recorded as per Case Record Form. Adverse effects like metallic taste, epigastric distress, abdominal pain, nausea, vomiting, diarrhea and constipation were specifically recorded as mild, moderate or severe.

Statistical Methods:- [6]

Sample size:-

All patients who fulfilled the criteria were included in the study within the one and half month's period of data collection and these patients were followed up for 12 weeks regularly. Initially 68 patients were included in the study. Out of these, 18 patients dropped out because of adverse effects and other personal reasons. Remaining 50 patients were divided into three groups each containing 25 patients and

were followed up regularly. Data was expressed as mean \pm SD.

Efficacy analysis:-

Change in haemoglobin which was the primary efficacy variable and the secondary efficacy variables like P.S. and E.S.R. observed during the study period in Carbonyl Iron group was compared with the Ferrous Sulfate group.

For determining individual efficacy of each compound 'Paired t test' (Student's t - test) with degree of freedom (df) 24 was used and for comparing the efficacy between the two

compounds 'Unpaired t test' with df 48 was used.

Safety analysis:-

Adverse drug reactions (ADRs) observed between two compounds were compared by using 'Chi-square (χ^2) test' with df 1.

Level of significance:

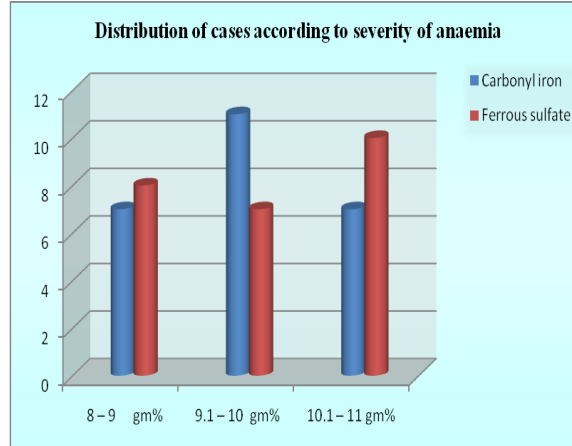
For all statistical tests a 'p' value of less than 0.05 was considered as significant and a 'p' value less than 0.001 was considered as highly significant.

A 'p' value more than 0.05 was considered as insignificant.

RESULTS

Table No.1: Distribution of cases according to severity of anaemia
(Group A – Carbonyl Iron, Group B- Ferrous Sulfate)

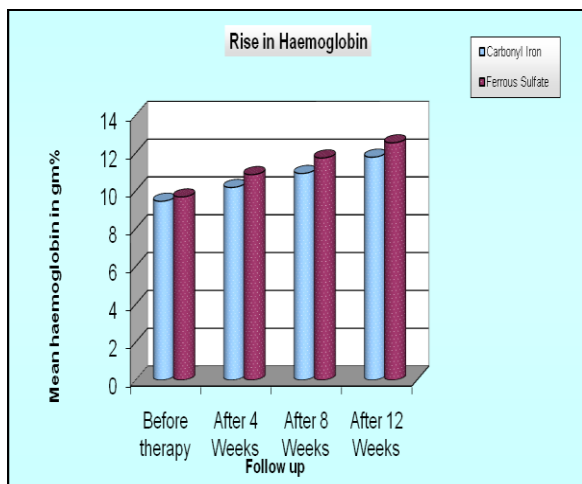
Hb range gm%	Group-A	Group-B
8 – 9 gm%	7	8
9.1 – 10 gm%	11	7
10.1 – 11 gm%	7	10
Total	25	25



➤ The above table & graph shows that in Group-A there were 11 patients with Hb. between 9.1–10 gm% and 7 patients with Hb. > 10.1 gm% while in Group-B there were 7 and 10 patients in that range respectively.

Table No.2: Mean Haemoglobin level on follow up-

Hb. level (gm%)	Group A	p Value (Paired 't')	Group B	p Value (Paired 't')
Before therapy	9.45	---	9.68	---
After 4 Weeks	10.18	<0.001	10.86	<0.001
After 8 Weeks	10.92	<0.001	11.74	<0.001
After 12 Weeks	11.78	<0.001	12.54	<0.001

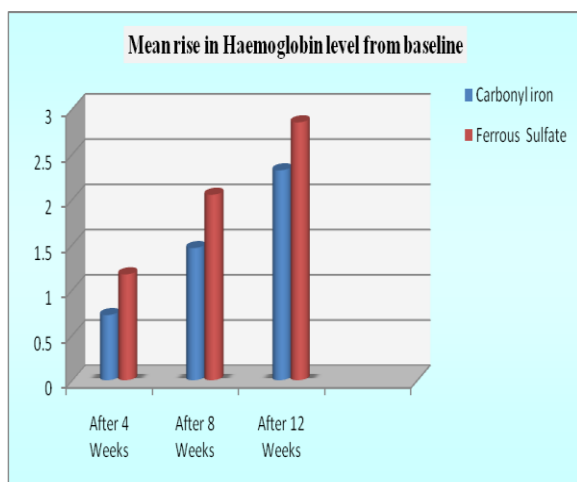


➤ The above table & graph collectively shows the mean Hb. level before therapy and on follow up after 4, 8 & 12 weeks in the two groups.

➤ It is clearly seen that the individual efficacy of both the compounds is very good and the rise in Hb level on follow up is statistically highly significant ($p < 0.001$)

Table No. 3: Comparison of Mean rise in Haemoglobin level from baseline between Group-A and Group-B on follow up

Mean rise in Hb.	Group- A	Group-B	p Value (Unpaired 't')
After 4 Weeks	0.72	1.17	< 0.02
After 8 Weeks	1.46	2.05	< 0.05
After 12 Weeks	2.32	2.85	< 0.10

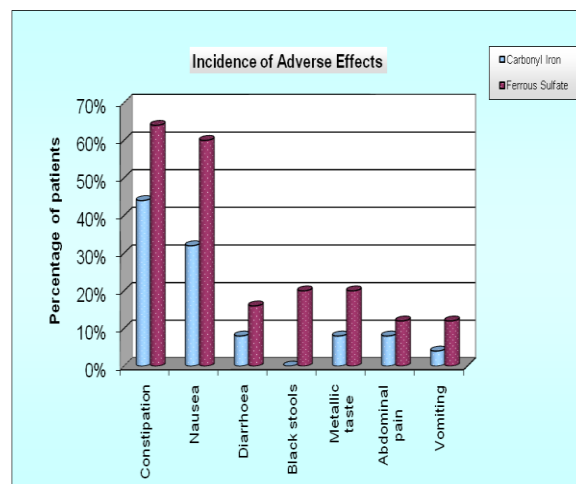


➤ At follow up after 4 wks and 8 wks the mean rise in Hb from baseline was significantly higher in case of Ferrous Sulfate than Carbonyl Iron which can be seen from above table. (p value < 0.02 and < 0.05 respectively)

➤ At the end of the study (after 12 wks) mean rise in Hb. from baseline was higher in case of Ferrous Sulfate but it was statistically insignificant. (p value < 0.10)

Table No.4: Comparison of safety between Group A and Group B

Adverse effects observed	No. of patients		p Value (χ^2 test)
	Group A	Group B	
Nausea - mild	7 (28%)	10 (40%)	> 0.05
- moderate	1 (4%)	5 (20%)	
Constipation -mild	11 (44%)	10 (40%)	> 0.05
- moderate	---	4 (16%)	
- severe	---	2 (8%)	
Diarrhoea	2 (8%)	4 (16%)	--
Abdominal pain	2 (8%)	3 (12%)	--
Vomiting	1 (4%)	3 (12%)	--
Metallic taste	2 (8%)	5 (20%)	--
Black stools	---	5 (20%)	--



➤ The above table & graph clearly shows that all adverse effects were more with Ferrous Sulfate than Carbonyl Iron. Four patients and two patients from Ferrous Sulfate group suffered from moderate and

severe constipation respectively which was mild in case of Carbonyl Iron.

➤ In addition to that five patients from Ferrous Sulfate group complained of black stools which was absent in case of Carbonyl Iron group.

➤ Nausea and constipation between two groups were compared by using Chi-square

(χ^2) test. The difference was statistically insignificant. (p value > 0.05)

➤ Other adverse effects were not compared by using Chi-square (χ^2) test as the number of patients with adverse effects was less and hence the test was not applicable.

DISCUSSION

The treatment of IDA is directed at replenishing hemoglobin and compensating for the deficit in stored iron by supplying sufficient iron. Carbonyl Iron, a pure form of elemental iron widely used as a food additive has remarkably low toxicity and much larger doses are tolerated when compared with ionized forms of iron such as Ferrous Sulfate. Carbonyl does not refer to the composition of iron particles but rather to the manufacturing process in which the controlled heating of vaporized iron pentacarbonyl leads to the deposition of uncharged elemental iron as microscopic spheres of < 5 μ in diameter.^[7]

The present study compares the therapeutic efficacy and tolerability of Carbonyl Iron and Ferrous Sulfate. We had taken iron deficient adult anaemic patients from Medicine OPD.

68 patients were enrolled for the study, of which 50 followed-up regularly. Remaining 18 patients were dropped out because of adverse effects and other personal reasons. Group A comprised of 25 patients, who received Carbonyl Iron and Group B comprised of 25 patients, who received Ferrous Sulfate.

Mean Hb levels were calculated before therapy and after 4, 8 and 12 weeks of therapy and it was observed that there was significant rise in haemoglobin level with both the groups. Thus individual efficacy of each compound was very good. This means that both the compounds were

effective in treatment of iron deficiency anaemia.

Two patients on Carbonyl Iron showed very poor response (rise was only up-to 0.2 gm %). In one patient final Hb. was reduced by 0.4 gm%. Maximum response obtained with Carbonyl Iron was increase in Hb. by 4 gm%.

Two patients on Ferrous Sulfate showed very poor response (rise was only up-to 0.2 gm %). In one patient final Hb. was reduced by 0.3 gm%. Maximum response obtained with Ferrous Sulfate was increase in Hb. by 4.3 gm%.

At the end of the study i.e. after 12 wks, the mean rise with Carbonyl Iron was 2.32 ± 0.92 and with Ferrous Sulfate was 2.85 ± 1.17 . Thus the mean rise was higher with Ferrous Sulfate than Carbonyl Iron (p value < 0.10), although that was statistically insignificant.

On comparing the tolerability of the two compounds, the results for Ferrous Sulfate were discouraging. Higher incidence of gastrointestinal side effects was observed with it. Similar observations were made by Hallberg L et al.^[8] Increased incidences of adverse effects with FS may be due to release of free radicals, which leads to cell damage and cell death. This was the reason for reduced compliance with FS in the present study. Fourteen patients left the trial because of intolerance to FS.

Similarly on comparison with Carbonyl Iron, the incidence of adverse effects was higher with Ferrous Sulfate.

Similar observations were reported by Gordeuk V R et al. [7]

It was also observed that greater the degree of anaemia, faster is the rise in haemoglobin on treatment. Driggers D A et al [9] and Pollit E et al [10] reported similar observations.

Iron deficiency anaemia is widely prevalent especially in the developing countries like India and it is a major public health problem in children and pregnant females, who represent a special population. This population cannot be neglected.

The present study shows that Carbonyl Iron is better alternative to FS as far as safety & tolerability is concerned. These are the major factors in compliance, especially when patients are taking oral iron preparations.

In the present study sample size was small because of negligence of patients towards IDA and reluctance for investigations. Hence further studies with large patient populations are required to strengthen the evidence of the present study. The more accurate but expensive investigations like serum iron, serum ferritin, total iron binding capacity (TIBC) and transferrin saturation were also not done because of cost factor.

CONCLUSIONS

To conclude the present study, individual efficacy of both compounds was very good and both compounds were effective in treatment of iron deficiency anaemia.

Efficacy of Ferrous Sulfate was higher than Carbonyl Iron.

Tolerability of Carbonyl Iron was better than Ferrous Sulfate.

The results of the present study suggest that Carbonyl Iron can be considered as a useful alternative formulation for the treatment of iron deficiency anaemia in patients who cannot tolerate Ferrous Sulfate.

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