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Original Article

Comparison of Efficacy and Tolerability of Ferrous Sulfate and Carbonyl Iron in Iron Deficiency Anemia in Pregnant Woman

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Key words:
Iron deficiency anemia, haemoglobin, carbonyl iron, ferrous sulfate.

Abstract

Introduction: *Iron deficiency anemia in pregnancy is common and causes a huge burden globally. Bangladesh is known to have a high prevalence of iron deficiency anemia in pregnant women. Hence, it is important to evaluate the efficacy and tolerability of drugs in treatment of iron deficiency anemia in pregnancy.*

Objective: *The purpose of present study was to compare the efficacy and tolerability of Ferrous Sulfate and Carbonyl Iron in Iron Deficiency Anemia in pregnant women.*

Methodology: *An observational prospective study was conducted in obstetric and gynae out – patient department of Sir Salimullah Medical College and Mitford Hospital. Woman between 16 – 28 weeks of pregnancy with haemoglobin level 7 – 10 g/dl with microcytic hypochromic blood film were included in this study. Pregnant women in 1^{st} and 3^{rd} trimester of pregnancy were excluded from the study. Among the study population one group was given Tablet Ferrous Sulfate and another group was given Capsule Carbonyl Iron.*

Results: *There was significant and comparable rise in HB in 4^{th}, 8^{th} and 12^{th} week in the two group. ($p<0.001$). Carbonyl iron showed significantly more rise in Hb as compared to Ferrous Sulfate. Adverse effects were seen more in number and intensity with Ferrous Sulfate. Individual efficacy of both compounds was good but Carbonyl Iron was better tolerated.*

Conclusion: *Carbonyl Iron is more effective and tolerable than Ferrous Sulfate in treatment of iron deficiency anemia in pregnancy.*

Introduction

As per World Health Organization (WHO), anemia in pregnancy is defined as haemoglobin concentration less than 11 g/dl. It is responsible directly or indirectly for 40 – 60% of maternal deaths from cardiac failure, hemorrhage, infection and pre-eclampsia. It also increases perinatal morality and morbidity rates consequent of preterm deliveries, intra-uterine growth restriction, low iron stores, iron deficiency anemia, cognitive and affective dysfunction in infant.[1]

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Incidence of iron deficiency anemia (IDA) is being particularly high in many underdeveloped tropical countries where it remains a major contributing factor to maternal morbidity and mortality and also high perinatal mortality. Iron deficiency is the commonest cause of anemia in pregnancy.[2]

A recent estimate based on World Health Organization (WHO) criteria indicated that around 600 – 700 million people worldwide have marked iron deficiency anemia (IDA) and the bulk of these people live in developing countries like Bangladesh.

In developed countries, prevalence of Iron deficiency anemia is much lower and usually varies between and 2% to 8%. In developing countries upto 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.[3]

The requirement of iron increase during pregnancy, specially in the third trimester. A pregnant woman needs six times more iron than a nonpregnant woman. Increased iron requirements to supply the expanding blood volume of the mother and the rapidly growing fetus and placenta can cause Iron Deficiency Anemia.[2]

Maternal Iron Deficiency Anemia early in pregnancy can result in low birth weight subsequent to preterm delivery as well as association exists between maternal anemia and lower infant apgar score. Therefore, iron supplementation is mandatory to improve or maintain the iron status of the mother during pregnancy.[2]

Plenty of oral iron preparations are available. Iron salts like ferrous sulphate, ferrous fumarate and ferrous gluconate are extensively prescribed for the prevention and treatment of iron deficiency. Carbonyl Iron is a pure form of elemental iron which was mainly used for the fortification of foods. Bioavailability of iron supplements increases with the increasing dose.[4]

However, gastrointestinal disturbances like nausea, constipation, vomiting, black stool, metallic taste and diarrhea are commonly associated with ingestion of iron salts. Food and chelating drugs in the gastrointestinal tract may interfere with rate of absorption and decrease the bioavailability of iron. This leads to variability in the haemoglobin correction during anemia in pregnancy. So, limitations of conventional iron salts have resulted in emergence of newer oral iron preparations like Carbonyl iron, Iron polymaltose complex, Ferrous ascorbate, Sodium feredetate and Ferrous bisglycinate.[5]

A mild deficiency should not affect baby while pregnancy. But if mild iron deficiency anemia goes untreated and becomes more severe during pregnancy is linked to an increased risk of a baby being born with a low birth weight. Having severe iron deficiency anemia may even increase the risk of still birth and newborn death. It is responsible directly or indirectly for 40% - 60% of maternal deaths from cardiac failure, hemorrhage, infection and preeclampsia.[1]

Methodology

Study Design and Place: This observational prospective study was conducted in the department of Pharmacology and Therapeutics in Sir Salimullah Medical College, Dhaka with the study period from July 2016 – June 2017.

Study Population: All pregnant women with Iron deficiency anemia attending the obstetric and gynae out patient department of Sir Salimullah Medical College and Mitford Hospital those were prescribed Ferrous Sulfate and Carbonyl Iron were included in the study population which was 160. They were selected on the basis of inclusion and exclusion criteria. Women between 16 – 28 weeks of pregnancy with haemoglobin level of 7 – 10 gm/dl with microcytic hypochromic blood film were included in the study. Pregnant women in 1st and 3rd trimesters of pregnancy were excluded from the study.

Study Procedure: An observational prospective study was conducted in a tertiary care hospital in Bangladesh. New patient according to the selection criteria attending the outpatient department of obstetrics and gynae in Sir Salimullah Medical College and Mitford Hospital during the study period were considered for analysis. After proper counseling, the aim, objectives, risk and the procedure of the study were explained in details to the subjects. Only positive respondents were recruited as study subjects and were allowed to withdraw themselves from the study even after participation. Informed consent was obtained from

all participants. The study subjects were divided in two groups, Group A (n = 80) taking tablet Ferrous Sulfate (150 mg twice or thrice daily) supplied from the hospital and Group B (n = 80) taking capsule Carbonyl Iron (50 mg twice or thrice daily) were taken from the same pharmaceutical source. Hb% was measured on the day of enrollment and on the 2nd, 4th, 8th and the 12th week. Adverse effects were noticed during the therapy and summarized at the end of 12th week therapy both for Ferrous Sulfate and Carbonyl Iron. Tablet Ferrous Sulfate was given three times daily for the patient whose haemoglobin level was between 7.0 to 8.0 gm/dl and two times daily for the patient whose haemoglobin level was between 8.1 – 10 gm/dl. Capsule Carbonyl Iron was given three times daily for the patient whose haemoglobin level was between 7.0 – 8.0 gm/dl and two times daily for the patient whose haemoglobin level was between 8.1 – 10 gm/dl.

Statistical Analysis: All the findings were recorded, compiled, tabulated and analyzed. The data was expressed as mean ± SD for windows version 21. Unpaired 't' tests, paired 't' tests, Chi-Square tests were done as the test of significance and p value <0.05 was considered as significant. Statistical analysis was done by using Statistical Package of Social Service (SPSS). The summarized data were presented in the form of tables.

Results:

The research work was conducted in the Department of Pharmacology and Therapeutics, Sir Salimullah Medical College using a prospective observational study design. A total of 160 study subjects were enrolled from Sir Salimullah Medical College and Mitford Hospital and followed up at 2nd, 4th, 8th and 12th week of therapy. Group A comprised of 80 patients who received Ferrous Sulfate and Group B comprised of 80 patients who received Carbonyl Iron. Mean haemoglobin levels were calculated before therapy and after 2nd, 4th, 8th and 12th weeks of therapy. At the end of the study, after 12 weeks the mean rise of haemoglobin with Carbonyl Iron was 0.96 ± 0.31 and with Ferrous Sulfate was 0.48 ± 0.07. Thus, the mean rise was higher with Carbonyl Iron than Ferrous Sulfate group. Similar observation was also identified by Gordeuk VR et. al. On comparing the tolerability of two compounds, the result of non-compliance in patient who took Ferrous Sulfate were more as higher incidence of gastrointestinal side effects like nausea, constipation, metallic taste and black stool were observed. Gordeuk VR et. al reported the same findings in his study.

Table-I

Hb level of the study subjects (who received three doses at different follow ups in both groups (n = 52)

	Hb level		p-value
	FS (n = 25) [Mean ± SD	CI (n = 27) [Mean ± SD	
At 2 weeks	8.28 ± 0.84	8.51 ± 0.73	0.293ns
At 4 weeks	8.39 ± 0.84	8.72 ± 0.68	0.120ns
At 8 weeks	8.49 ± 0.84	8.96 ± 0.68	0.031*
At 12 weeks	8.66 ± 0.84	9.25 ± 0.66	0.006**

Unpaired t test was done to measure the level of significance. P value <0.05 was accepted as level of significance.

ns = non-significant; */**/*** = significant

Table I shows Hb level raises significantly in patients who took Carbonyl Iron (3 doses) after 12 weeks.

Table II

Hb level of the study subjects (who received two doses) at different follow ups in both groups (n = 108)

	Hb level		p-value
	FS (n = 55) Mean ± SD	CI (n = 53) Mean ± SD	
At 2 weeks	8.61 ± 0.80	8.73 ± 0.67	0.396ns
At 4 weeks	8.72 ± 0.81	8.93 ± 0.65	0.144ns
At 8 weeks	8.85 ± 0.81	9.18 ± 0.63	0.019*
At 12 weeks	8.99 ± 0.81	9.44 ± 0.63	0.002**

Unpaired t test was done to measure the level of significance. P value 0.05 was accepted as level of significance.

ns = non-significant; */**/*** = significant

Table II shows Hb level rises significantly in patients with who took Carbonyl Iron (2 doses) after 12 weeks.

Table III

Hb level of study subjects at baseline and after treatment at different follow ups in both groups (n = 160)

	Hb level		
	FS (n = 80) Mean ± SD	CI (n = 80) Mean ± SD	p-value
Pre treatment	8.41 ± 0.83	8.42 ± 0.73	0.895^{ns}
At 2 weeks	8.51 ± 0.82	8.66 ± 0.69	0.214^{ns}
At 4 weeks	8.62 ± 0.82	8.86 ± 0.67	0.043*
At 8 weeks	8.74 ± 0.83	9.11 ± 0.65	0.002**
At 12 weeks	8.89 ± 0.83	9.38 ± 0.64	<0.001***

Unpaired t test was done to measure the level of significance. P value < 0.05 was accepted as level of significance.

ns = non-significant; */**/*** = significant

Table III shows rise of Hb level was statistically significant compared to pre treatment value.

Table IV

Rise of Hb level of the study subjects after treatment at different follow ups in both groups (n = 160)

	Rise in Hb level		
	FS (n = 80) Mean ± SD	CI (n = 80) Mean ± SD	p-value
At 2 weeks	0.10 ± 0.04	0.24 ± 0.26	<0.001***
At 4 weeks	0.21 ± 0.05	0.44 ± 0.30	<0.001***
At 8 weeks	0.33 ± 0.06	0.68 ± 0.28	<0.001***
At 12 weeks	0.48 ± 0.07	0.96 ± 0.31	<0.001***

Unpaired t test was done to measure the level of significance. P value <0.05 was accepted as level of significance.

ns = non-significant; */**/** = significant

Table IV shows at the end of the study (after 12 weeks) the mean rise of Hb with Carbonyl Iron was higher than with Ferrous Sulfate

Table V

Distribution of study subjects according to adverse effects in both groups (n = 160)

	Group		
	FS (n = 80)	CI (n = 27)	p-value
Nausea			
Mild	29 (36.3)	22 (27.5)	0.004**
Moderate	15 (18.8)	4 (5.0)	
Constipation			
Mild	27 (33.8)	35 (43.8)	<0.001***
Moderate	12 (15.0)	0 (0.0)	
Severe	5 (6.3)	0 (0.0)	
Diarrhea	11 (13.8)	6 (7.5)	0.200^{ns}
Abdominal pain	9 (11.3)	5 (6.3)	0.263^{ns}
Vomiting	8 (10.0)	3 (3.8)	0.118^{ns}
Metallic taste	15 (18.8)	6 (7.5)	0.035*
Black stool	13 (16.3)	0 (0.0)	

Chi square test was done to measure the level of significance. P value <0.05 was accepted as level of significance.

ns = non-significant; */**/*** = significant

Table V shows the adverse effects were observed more with Ferrous Sulfate group than the Carbonyl Iron Group.

Discussion

As we know iron deficiency anemia is very common worldwide. A recent estimate based on WHO criteria indicated that around 600 – 700 million people world wide have marked Iron deficiency anemia (IDA) and the bulk of these people live in developing countries like Bangladesh. Pregnancy with anemia has a significant impact on the health of fetus as well as that of the mother. The treatment of Iron deficiency anemia (IDA) is given to replenish Hb and restore iron stores by supplying sufficient iron.

Routine iron supplementation with iron salts shows low efficacy for the control of Iron deficiency anemia (IDA) due to poor compliance with the treatment, because of its disagreeable flavor and adverse effects such as constipation, metallic taste, black stool, nausea, vomiting, diarrhea.

Among the possible alternatives to control iron deficiency, Carbonyl Iron is formulated in such a way that it has remarkably low toxicity when compared with ionized form of iron such as Ferrous Sulfate.

Carbonyl iron 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 < 5μ in diameter.[6]

Ferrous Iron is absorbed shortly after it is ingested. But Carbonyl Iron is only absorbed at the rate of gastric acid production as it is required to make Carbonyl Iron soluble. This means Carbonyl Iron enters the system much more gradually than other types of Iron that can dissolve rapidly.

The present study compared the therapeutic efficacy and tolerability of Ferrous Sulfate and Carbonyl iron.

160 patients were enrolled for the study and followed up at 2nd, 4th, 8th, and 12th week of therapy. Group-A comprised of 80 patients, who received Ferrous Sulfate and Group B comprised of 80 patients, who received Carbonyl iron.

Mean Hb levels were calculated before therapy and after 2, 4, 8, and 12 weeks of therapy. At the end of the study, after 12 weeks the mean rise of Hb with Carbonyl iron was 0.96 ± 0.31 and with Ferrous sulfate was 0.48 ± 0.07. Thus, the mean rise was higher with Carbonyl iron than Ferrous sulfate group. Gordeuk VR et al. reported similar observation.

On comparing the tolerability of the two compounds, the results of non-compliance in patients who took Ferrous sulfate were more as higher incidence of gastrointestinal side effects like nausea, constipation metallic taste and black stool were observed. Similar observations were made by Gordeuk VR et al.

Conclusion

The study shows that individual efficacy of both compounds was good and they were effective in the treatment of iron deficiency anemia in pregnancy. Efficacy of Carbonyl Iron was higher than Ferrous Sulfate. Tolerability of Carbonyl Iron was better than Ferrous Sulfate. The result of the present study suggest that Carbonyl Iron can be considered as a useful alternative formulation for the treatment of iron deficiency anemia in patients due to its better efficacy and tolerability.

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