

Comparative Study on Efficacy, Tolerability and Cost of Different Iron Supplements among Ante Natal Women with Iron Deficiency Anaemia

Sudakshina K¹, Sakthibalan M^{1*}, S Arthi², Mangaiarkkarasi A¹

¹Department of Pharmacology, Sri Venkateshwaraa Medical College Hospital & Research Centre, Puducherry, India

²Department of Obstetrics and Gynaecology, Sri Venkateshwaraa Medical College Hospital & Research Centre, Puducherry, India

ABSTRACT

Introduction: Anaemia is one of the commonest medical complications encountered during pregnancy. India is among the countries with maximum prevalence of anaemia in the world. The commonly used treatment for iron deficiency anaemia is oral iron preparations like ferrous sulphate, ferrous gluconate, ferrous ascorbate, ferrous fumarate and parenteral iron sucrose.

Aim: To assess the Mean change in the haemoglobin levels from baseline upto 60th day of treatment with different iron supplements and to assess its cost effectiveness ratio.

Materials and Methods: This was a prospective interventional clinical end point study conducted at Sri Venkateshwaraa Medical College Hospital and Research centre, Puducherry, India, from December 2019 to December 2020, among eighty four ante natal women (>14 weeks) with iron deficiency anaemia. After getting Ethics committee approval, the participants who fulfilled the inclusion and exclusion criteria were randomized to respective treatment groups. Group 1 (n=21) received Ferrous sulphate 200 mg, Group 2 (n=21) received Ferrous ascorbate 200 mg, Group 3 (n=21) received Ferrous fumarate 200 mg twice daily for a period of 60 days and Group 4 (n=21) received Iron sucrose 200 mg, based on iron requirement in divided doses and administered once in two weeks for a period of 60 days. Haemoglobin, RBC count, MCV, MCH, MCHC, WBC, Platelet count and cost of the treatment were assessed before and at the end of 60 days. Data were analysed using Graph Pad Prism software version 7.0 using Students 't' test and one way ANOVA.

Results: We observed a significant ($P < 0.001$) rise in the mean haemoglobin level from 10.4 ± 0.4 , 10.4 ± 0.5 , 10.4 ± 0.5 and 8.5 ± 0.3 to 11.2 ± 0.6 ($P = 0.0001$), 11.1 ± 0.6 ($P = 0.0001$), 11.3 ± 0.8 ($P = 0.0001$) and 10.9 ± 0.6 ($P = 0.0001$) in group 1, 2, 3 and 4 respectively. The average cost effectiveness ratio, with respect to group 1, 2, 3 and 4 was Rs. 675, Rs. 1782.9, Rs. 1110.7 and Rs. 786.7 per increase in Hb % respectively.

Conclusion: The outcome of this study proved the effective role of various oral ferrous iron preparations and all of them were found to be equally efficacious in improving the haemoglobin concentration. But the injectable Iron sucrose showed a significant improvement in mean hemoglobin percentage compared to the various oral preparations. But, on analyzing the cost Effectiveness ratio, it was found out that the cost incurred per increase in HB% was less in ferrous sulphate group followed by Iron sucrose, ferrous fumarate and ferrous ascorbate. The results of this study can be helpful in pharmaco-economical decision making while selecting a cost effective iron supplement for treating iron deficiency anemia.

Key words: Ferrous sulphate, Hemoglobin, Iron sucrose, Pharmaco-economical

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Corresponding author: Sakthibalan M

e-mail: saheerose@gmail.com

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INTRODUCTION

Anaemia is one of the commonest medical complications encountered during pregnancy. India is among the countries with maximum prevalence of anaemia in the world [1-3]. Prevalence of Iron deficiency anaemia

among pregnant women was found to be 58%, non-pregnant, non-lactating women was 50% and adolescent girls was 56% as per the National Family Health Survey-3 in 2007[4]. It has also been estimated that around 20 to 40% of maternal deaths in India are due to anaemia and its complications. Anaemia also contributes to about 50% of Global Maternal Deaths. As per WHO, Iron deficiency anaemia is 3rd leading cause of Disability Adjusted Life year lost for females in the age group of 15 to 44 years. WHO datasheet presents, prevalence of anaemia in pregnant women is 51% in developing countries [3-7]. Anaemia in pregnant woman is a Public health issue [8]. According to WHO out of the 529000 maternal deaths occurring every year, 136000 or 25.7% of it takes place in India, where two-thirds of maternal deaths occur after delivery. The daily requirements of iron increase due to physiological changes in pregnancy, as in the third trimester, a pregnant woman requires six times more iron than a non-pregnant woman [9-12]. Iron supplementation are strongly recommended to improve and maintain the iron status of the pregnant mother [13,14]. Government of India recommends 200 mg of elemental iron with 1mg folic acid from second half of pregnancy for a period of 100 days and also post-partum [15,16].

The commonly used oral iron preparations are ferrous sulphate, ferrous gluconate, ferrous ascorbate and ferrous fumarate, etc. However, oral iron supplementations frequently lead to various adverse effects. Parenteral iron therapy like iron sucrose, iron dextran and ferric carboxy maltose are reserved as an alternative to oral iron therapy for patients with severe iron deficiency anaemia and those who are unable to tolerate or absorb oral iron preparations [16,17]. Since these Iron preparations are to be taken for a longer period, their cost of therapy is also a major concern in developing countries like India. Literature review shows that certain studies are in favour of usage of carbonyl iron instead of ferrous form. Studies are also in favour of ferrous form and injectable iron preparations [16-21]. India drug market is swamped with more than 7000 drug formulations. Among these, 621 formulations were listed as hematinic [17]. The cost of the oral iron formulations for providing 100 mg elemental iron ranged from Rs. 0.14 to Rs.183.25 [17]. Pharmacoeconomic Evaluation is not only a means to find the least expensive alternative drug, but it is also a comparison tool which will evaluate various treatment options quantitatively and objectively based on a defined model which has not been studied in scope for Iron preparations so far. Conventional iron Preparations are cheaper when compared to newer iron preparations, which is 4 to 5 times costlier. Cost is one of the major determining factors for patient compliance, particularly in low socioeconomic developing country like India [17,22,23]. Studies have shown that different oral ferrous iron supplements were equally efficacious, while other studies contradict the statement and they are in favour of specific iron preparations like ferrous fumarate and iron polymaltose complex, while some

were in favour of parenteral iron preparations compared to oral iron therapy [17,19,21,24,25]. The concept of cost effectiveness is still a debate with regard to use of various iron preparations during Pregnancy.

Therefore, a comparative study on different oral and parenteral iron supplements was planned to assess the Mean change in the haemoglobin levels from baseline up to 60th day in ante natal women and also to analyse the cost effectiveness with their tolerability profiles, as this can influence the patient compliance and the therapeutic outcome.

MATERIALS AND METHODS

This was a prospective interventional clinical end point study conducted among eighty four antenatal women (>14 weeks) with iron deficiency anaemia over a period of 12 months between February 2019 to February 2020 at Sri Venkateshwaraa Medical College Hospital and Research centre which is tertiary care hospital in, Puducherry.

Eighty four patients were selected by convenient sampling method. Sample size was calculated considering alpha 5%, Power of the study 80%, expected change in mean Hb difference 0.5 gm%, Standard deviation of 0.78 [16] minimum sample size required was 21 per group).

Ante natal women (>14 weeks) in the age group of 18 to 40 years with Haemoglobin levels between 9 - 11gm/dl and after confirming Iron deficiency status by performing peripheral smear were included in this study. Ante natal women of less than 14 weeks of gestation or with complications like bleeding piles, excessive emesis, active peptic ulcer, diabetes, hypertension, eclampsia, hypothyroidism, hyperthyroidism and multiple pregnancies and with history of oral/parenteral iron intolerance were excluded from the study.

All the participants who fulfilled the inclusion and exclusion criteria were recruited and randomized to respective groups, after getting a written informed consent. Convenient sampling method was adopted. The study was approved by the Scientific research committee & Institutional Ethics Committee of our Institute (IEC No: SVMCH/IEC/2019/Feb-25). The study was registered in CTRI: Ref. no. CTRI/2019/09/021380 (<http://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=36964&EncHid=61426.17438&modid=1&compid=19>) . Confidentiality was maintained throughout the study.

Group 1(n=21) received Ferrous sulphate 200 mg (Feosol) twice daily orally after food for a period of 60 days.

Group 2 (n=21) received Ferrous ascorbate 200 mg (Orofer) twice daily orally after food for a period of 60 days.

Group 3(n=21) received Ferrous fumarate 200 mg (Livogen) twice daily orally after food for a period of 60 days.

Group 4(n=21) received Iron sucrose 200 mg (I Max) (as per Hb deficiency status the iron requirement dose was calculated) intra venous preparation after test dose (0.1 ml to rule out hypersensitivity), in divided doses as per the iron requirement, was administered once in 15 days for a period of 60 days.

The baseline characteristics like age, BMI (body mass index) and gestational age were recorded before administering the supplement.

5 ml of venous blood was collected under aseptic precautions in vacutainer containing EDTA for the estimation of Complete blood count and Peripheral smear. Complete blood count was done by autoanalyser-Mindray M52.

Baseline Haemoglobin, RBC count, WBC count, Platelet count, MCV(Mean corpuscular volume), MCH (Mean corpuscular hemoglobin), MCHC (Mean corpuscular hemoglobin concentration), Peripheral smear(for confirming iron deficiency anaemia) and details of drugs prescribed were recorded.

Milk and milk products were restricted for a period of 1 hour post administration. Proper nutritional food advice was given for all participants. The participants were followed up for 60 days duration and at the end of the study period the demographic characters and blood count analysis were repeated to assess the mean change from baseline values.

The cost of the different iron preparations used was obtained from the hospital Pharmacy and total drug cost (direct medical cost) for 60 days was calculated. The other indirect costs were not taken into consideration for estimation of cost involved.

The ratio between the cost and Effectiveness was estimated by dividing the total drug cost for 60 days by the mean change in haemoglobin concentration for all the four groups and compared statistically.

Tolerability of the given iron supplements were also assessed during each follow up visits on day 30 and day 60, by monitoring adverse drug reactions during the study period. There were no funding for this study and there is no conflict of interest.

Statistical analysis

Quantitative data (age, Haemoglobin, RBC count, MCV, MCH, MCHC) collected were presented with Mean and Standard deviation. Paired and unpaired Student 't' test and one way ANOVA followed by Bonferroni test

was used to analyse the significant difference between the pre and post treatment blood indices. Data were analysed using Graph Pad Prism software version 7.0. P value <0.05 was considered as statistically significant.

RESULTS

In this study, eighty-four antenatal women who satisfied the inclusion and exclusion criteria were recruited and all of them completed the study procedure. There was no statistically significant difference observed between the four groups with respect to the mean age, gestational age and BMI on baseline (Table 1).

We observed a significant (P=0.001**)increase in the mean haemoglobin level from 10.4 + 0.4, 10.4 + 0.5, 10.4 + 0.5 and 8.5 + 0.3 to 11.2+0.6, 11.1 +0.6, 11.3 +0.8 and 10.9+ 0.6 in groups 1,2,3,and 4 respectively. On inter group comparison using ANOVA followed by Bonferroni test, it was found that there is significant improvement in the mean change in haemoglobin concentration only in group 4 when compared with group 1,2 and 3 (Table 2).

The average cost effectiveness ratio, with respect to Group 1(Ferrous Sulphate), Group 2(Ferrous ascorbate), Group 3 (Ferrous Fumarate) and Group 4 (Inj. Iron Sucrose) is Rs. 675, Rs. 1782.9, Rs. 1110.7 and Rs. 786.7 per increase in Hb% respectively. Thus, ferrous sulphate can be considered as cost effective with a cost effectiveness ratio of Rs. 675 per % increase in hemoglobin (Table 2). There was a significant improvement in the RBC count, MCV, MCHC and MCH parameters from baseline to end of treatment in all the groups (Tables 3 and 4).

There were no significant changes observed with respect to the WBC and Platelet counts after treatment with different iron supplements (Table 5). There were no documented serious adverse effects during the entire study period. There was a statistically significant difference between the groups (inter group analysis), on applying two tailed t test. The common gastrointestinal adverse effects observed were nausea, vomiting and gastritis. Ferrous sulphate treated group had the least number of adverse effects and ferrous fumarate treated group had the maximum number of adverse effects. There is significantly higher number of adverse effects noted in ferrous fumarate group. No hypersensitivity reactions were observed in all groups as shown in Table 6. With regard to Compliance, there was 100% compliance in all the treatment groups. There were no missed doses in any of the treatment groups.

Table 1: Demographic details.

Groups	Age (in years)	Gestational age (in weeks)	BMI (kg/m ²)
	Mean (SD)	Mean (SD)	Mean (SD)
Group 1 (Ferrous sulphate)	24 (4.2)	24.3(1.8)	23.8(1.6)
Group 2 (Ferrous ascorbate)	24.7(3.3)	23.1(1.7)	24.1(1.9)
Group 3 (Ferrous fumarate)	25(4.1)	23.8(1.5)	24.5(3.1)
Group 4 (Inj. Iron Sucrose)	26(4.7)	24(1.5)	25.1(2.0)
P Value	0.466	0.107	0.268

ANOVA was used for intergroup comparison. P value <0.05 was considered statistically significant

Table 2: Percentage improvement in haemoglobin (Hb) and its cost effectiveness.

Groups	Hb Before Treatment	Hb After Treatment	p-value*	Mean Diff. (CI)	Hb Improvement (Percentage)	Average increase in HB Concentration over 60 days	Cost of therapy for 60 days (in Rupees)	Cost effectiveness ratio
	Mean (SD) gm%	Mean (SD) gm%						
Group 1 (Ferrous sulphate)	10.4 (0.4)	11.2(0.6)	P<0.001**	0.53 (0.30 - 0.75)	7.7 (%)	0.8	540	675
Group 2 (Ferrous ascorbate)	10.4(0.5)	11.1(0.6)	P<0.001**	0.73 (0.43-1.03)	6.7 (%)	0.7	1248	1782.9
Group 3 (Ferrous fumarate)	10.4(0.5)	11.3(0.8)	P<0.001**	0.92 (0.58-1.26)	8.7 (%)	0.9	999.6	1110.7
Group 4 (Inj. Iron Sucrose)	8.5(0.3)	10.9(0.6)	P<0.001**	2.34 (2.05-2.63)	31.3 (%)	2.4 (p < 0.001**)	1888	786.7

Paired t- test was applied to compare the improvement within the groups and ANOVA followed by Bonferroni test was used to compare the intergroup improvement in haemoglobin concentration. P value <0.05 was considered statistically significant. ** P < 0.001

Table 3: Mean improvement in RBC count and MCV.

Groups	RBC count Before Treatment Mean (SD) million/cu.mm.	RBC count After Treatment Mean (SD) million/cu.mm	p-value	MCV Before Treatment Mean (SD) fL	MCV After Treatment Mean(SD) fL	p-value
Group 1 (Ferrous sulphate)	3.8 (0.2)	4.1 (0.3)	P<0.001**	70 (6)	85 (6)	P<0.001**
Group 2 (Ferrous ascorbate)	3.7(0.3)	4.0(0.2)	P<0.001**	73 (4)	84 (5)	P<0.001**
Group 3 (Ferrous fumarate)	3.7 (0.3)	4.0 (0.3)	P<0.001**	77 (6)	88 (6)	P<0.001**
Group 4 (Inj. Iron Sucrose)	3.2 (0.1)	3.8 (0.2)	P<0.001**	63 (3)	78 (4)	P<0.001**

Paired t- test was applied to compare the improvement within the groups. P value <0.05 was considered statistically significant. ** P < 0.001. There was no significant difference noted between the groups on applying ANOVA.

Table 4: Improvement in MCHC and MCH.

Groups	MCHC Before Treatment Mean (SD) g/dl	MCHC After Treatment Mean (SD) g/dl	p-value	MCH Before Treatment Mean (SD) Pg	MCH After Treatment Mean (SD) pg	p-value
Group 1 (Ferrous sulphate)	30 (1)	33 (2)	P<0.01*	28 (1)	31 (1)	P<0.01*
Group 2 (Ferrous ascorbate)	32 (1)	33 (2)	P<0.01*	29 (1)	32 (1)	P<0.01*
Group 3 (Ferrous fumarate)	31 (2)	32 (2)	P<0.001*	28 (3)	30 (3)	P<0.001*
Group 4 (Inj. Iron Sucrose)	31 (2)	33 (2)	P<0.01*	27 (1)	30 (2)	P<0.01*

Paired t- test was applied to compare the improvement within the groups. P value <0.05 was considered statistically significant. * P < 0.01, ** P < 0.001. There was no significant difference noted between the groups on applying ANOVA.

Table 5: WBC and platelet count.

Groups	WBC Before Treatment Mean (SD) cells/cu.mm	WBC After Treatment Mean (SD) cells/cu.mm	p-value	Platelet Before Treatment Mean (SD) Cells/ μ l	Platelet After Treatment Mean (SD) Cells/ μ l	p-value
Group 1 (Ferrous sulphate)	7780.95 (1394.14)	7614.9 (1798.69)	P>0.05	297733.7 (76529.6)	295285.5 (65866.5)	P>0.05
Group 2 (Ferrous ascorbate)	6451.42 (1446.82)	6604.42 (1502.87)	P>0.05	283714.3 (81536.5)	284571.1 (95335.61)	P>0.05
Group 3 (Ferrous fumarate)	6826.66 (1398.3)	6916.82 (1213.9)	P>0.05	293614.5 (61436.5)	296674.3 (75431.7)	P>0.05
Group 4 (Inj. Iron Sucrose)	6886.19 (1444.7)	7001.8 (1425.4)	P>0.05	279824.2 (64278.9)	282371.0 (85329.85)	P>0.05

Paired t- test was applied to compare the improvement within the groups and ANOVA was used to compare between the groups. P value <0.05 was considered statistically significant. There was no significant difference noted within or between the groups.

DISCUSSION

Anaemia during pregnancy has a significant influence on the health of the foetus and mother due to iron utilization

by the foetus which takes the priority, followed by maternal hematocrit while the maternal iron stores are often depleted during the course of pregnancy. The mother indeed requires iron stores for lactation and

Table 6: Number of adverse effects observed during the study period in each group.

Group	Gastrointestinal adverse effects	Hypersensitivity	Total number of adverse effects	P value
Group 1(n=21)	13	0	13	*P=0.0014
Group 2 (n=21)	15	0	15	
Group 3 (n=21)	19	0	19*	
Group 4 (n=21)	14	0	14	

Two tailed t test was applied. The number of adverse events reported was significantly high in group 3(ferrous fumarate group) P value <0.05 was considered statistically significant.

future pregnancies too [12].

Treatment with Ferrous sulphate, ferrous ascorbate, ferrous fumarate and Iron sucrose has shown an increase in Haemoglobin levels by 0.8, 0.7, 0.9 and 2.4 gm%, The increase in haemoglobin was significant in Iron sucrose group. But on comparing the average cost effectiveness ratio it was observed that ferrous sulphate was cost effective with a ratio of Rs.675per % increase in hemoglobin. In this study there were also no documented serious adverse effects during the study period except for gastrointestinal side effects.

A previous study done by Eesha, et al. concluded that ferrous fumarate was a cost effective medication for treatment as well as prevention of Iron deficiency anemia in pregnancy based on its cost effectiveness analysis when compared with ferrous ascorbate and iron polymaltose complex. However, it was not compared with ferrous sulphate, which was compared in the present study [17].

A review done by Santiago, et al. stated that ferrous salts are the treatment of choice in iron deficiency anaemia considering their high effectiveness, tolerability and low cost [18]. Preparations with iron polymaltose generally have low bioavailability and their clinical efficacy is less. The superiority of some ferric iron preparations over ferrous sulphate preparations is also debatable. [18,19] Hence, ferrous salt preparations of iron can be considered to provide a better cost effective treatment for Iron deficiency anaemia, which is in concordance with our study results.

Study done by Saha, et al. concluded that iron polymaltose complex can be considered as a cost effective alternative to oral ferrous iron preparations in pregnancy [19]. Study done by Szarfarc, et al. highlighted the non-compliance taste in ferrous sulphate consumers [20]. But, in our study there were no reports of any non-compliance due to taste. The parenteral iron preparations are better than oral iron preparations in correcting the anemic status in 2nd and 3rd trimester of pregnancy as per the study done by Maheshwari, et al. [21]. Our study also found that parenteral iron sucrose administration showed a very good improvement in Haemoglobin by 2.4 gm%. But on calculating the average cost effectiveness ratio, the parenteral iron treatment was only second to oral ferrous sulphate treatment. The total number of adverse effects encountered with ferrous sulphate were less, compared to other iron preparations. Karelia, et al. noted that, there was a vast difference in cost of various iron preparations. Conventional iron Preparations were

cheaper compared to the newer iron preparations which were 4 to 5 times costlier [22]. Study done by Gamad, et al. compared the cost effectiveness of different oral iron formulations like ferrous sulfate, ferrous fumarate, ferrous ascorbate, and carbonyl iron in the treatment of iron-deficiency anemia in Ante natal women and found that all the formulations were equally effective in treating Iron deficiency anaemia and that they can be prescribed inter changeably [25]. Our study results are also showing equal efficacy of all oral iron preparations like Ferrous sulphate, ferrous fumarate and ferrous ascorbate, but on comparing the Cost, it was evident that Ferrous Sulphate was better among them.

Study done by Kochhar, et al. compared Intravenous iron sucrose versus oral ferrous sulphate preparations in the treatment of iron-deficiency anaemia in Ante natal women and found that parenteral iron sucrose is a safe treatment for correction of anaemia in ante natal women, without serious side-effects, as there was significant improvement in Haemoglobin levels in Iron sucrose group, but the study also highlighted that side effects were mild in ferrous sulphate group. But the Cost part was not assessed in it [24]. Our study results also highlighted that Iron sucrose showed a significant improvement in Haemoglobin levels when compared to other oral formulations, but on analyzing the cost effectiveness, it was found out that ferrous sulphate was better than Iron sucrose. Since cost is one of the major factors enhancing the drug compliance of the patient, particularly in developing countries like India, where iron deficiency anaemia is more prevalent. Especially during pregnancy iron supplements should be continued throughout pregnancy as well as postnatal period, which play a vital role in reducing the mortality and morbidity of mother and the foetus [21]. Thus, our study highlights on the cost and effectiveness of various oral and parenteral iron preparations commonly used in clinical practice in 2nd and 3rd trimester of pregnancy. However, further studies with large patient populations are required to strengthen the evidence of the present study.

LIMITATIONS

Only the total drug cost (direct medical cost) was considered in the study for evaluation of cost effectiveness and the patients were followed up only for 60 days, which were the limitations of this study.

CONCLUSION

The outcome of this study proved the effective role of

various oral ferrous iron preparations and all of them were found to be equally efficacious in improving the haemoglobin concentration. But the injectable Iron sucrose showed a significant improvement in mean hemoglobin percentage compared to the various oral preparations. On analyzing the cost Effectiveness ratio, it was found out that the cost incurred per increase in HB% was less in ferrous sulphate group followed by Iron sucrose, ferrous fumarate and ferrous ascorbate. This can be a factor which can improve the patient compliance. The results of this study can be helpful in pharmaco-economical decision making while selecting a cost effective iron supplement for treating iron deficiency anemia.

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