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Comparison of efficacy, tolerability, and cost of newer with conventional oral iron preparation

S.S. Patil[1*], C.C. Khanwelkar[2], S.K. Patil[3], V.M. Thorat[2], S.A. Jadhav[2] and A.V. Sontakke[4]

[1]Department of Pharmacology, Dr. D.Y. Patil Medical College, Kolhapur, Maharashtra, India,
[2]Department of Pharmacology, Krishna Institute of Medical Sciences Karad, Maharashtra, India,
[3]Department of Pathology (blood bank), Civil Hospital Kolhapur, Maharashtra, India and
[4]Department of Biochemistry, Krishna Institute of Medical Sciences Karad, Maharashtra, India

Abstract: *Background:* Iron deficiency anaemia in women of reproductive age group is a major health problem in India. *Objective:* The present study was designed to compare the efficacy, tolerability, and cost, of three oral iron preparations among the anaemic pregnant women (n=6o) of gestation (12-24 weeks). *Methodology:* The patients were divided into 3 groups (n=20) and treated with ferrous fumarate(100mg), ferrous bisglycinate (100mg),and carbonyl iron(100mg) respectively. Follow-up was done for 3 months. Haemoglobin gm%, mean corpuscular volume and reticulocyte count were assessed at 0,1,2,3 months and serum ferritin at 0 and 3 months. Adverse effects were monitored and cost analysis was done at end of three months. *Results:* Significant increase in Hb was seen in all three groups ($p<0.001$) but, no significant difference was found between three treatments in relation to increase in Hb. Increase in ferritin with ferrous fumarate was significantly more than other treatments ($p<0.05$). Nausea, vomiting, epigastric pain was significantly more with ferrous fumarate but patient compliance was not affected due to them. Ferrous fumarate was the cheapest amongst all three treatments. *Conclusion:* It can be concluded that, ferrous fumarate still can be considered best cost effective medication with tolerable side effects for treatment as well as prevention of iron deficiency anaemia in pregnancy.

Key words: ferrous fumarate, ferrous bisglycinate , carbonyl iron, hemoglobin, , serum ferritin.

Introduction

Iron deficiency anaemia is a major health problem world wide. Especially in women of reproductive age group, there is prevalence of anaemia. Factors like malnutrition, blood loss during menstruation and delivery, depletion of stores during pregnancy and nursing period, contributes to development of iron deficiency anaemia. WHO has accepted 11 gm% as the normal haemoglobin (Hb) level in pregnancy [1]. However in India and most of other developing countries the normal limit is often accepted as 10 gram percent. According to the WHO report, the prevalence of iron deficiency anaemia in pregnant women in developing countries is 35-75%. In India it is 65% in urban and 75% in rural area [2]. Anaemia has a significant impact on the health of the fetus as well as that of the mother. It impairs the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss and perinatal deaths and increased preterm labors [3].

The increased need of iron during pregnancy, specially after the second trimester makes iron supplementation mandatory [4]. Almost all cases of iron deficiency anaemia respond readily to treatment with iron supplementation. The most common iron salt used for oral administration is ferrous sulfate, but it is known to produce intestinal side effects (nausea, vomiting abdominal pain, constipation, diarrhea) in many users [5]. Ferrous fumarate has less gastrointestinal side effects and is readily absorbed than Fe sulfate [6]. Now different new iron salts are marketed which are claimed to have low gastrointestinal intolerance, therefore better patient compliance. Few of these newer preparations are also claimed to increase Hb level faster and as well as improve the iron storage better than conventionally used ferrous sulfate and ferrous fumarate. Therefore it was thought worth while to study the effects of one standard conventional oral iron preparation

ferrous fumarate and two new oral iron preparations, iron bisglycinate and carbonyl iron. Iron bisglycinate is a amino acid chelate and has shown great efficacy, less GI irritation and its absorption is not retarded by presence of phytates [7]. Second new iron preparation carbonyl iron which is highly purified metallic iron, particle size less than 5µ in diameter has slow but complete absorption and less side effects [8]. The purpose of this study is to find the best cost effective iron preparation out of three.

Material and Methods

Study sample: The study was conducted in Krishna institute of medical sciences (KIMS) Karad in the state of Maharashtra, India. It was designed as a prospective longitudinal study in 60 pregnant women that participated in prenatal checkup program with gestational period between 12 to 22 weeks having serum Hb less than 10gm% and were diagnosed microscopically to have microcytic hypocromic anaemia. Study protocol was approved by the institutional ethics committee KIMS Karad. After taking informed written consent, the subjects were randomly allocated into 3 groups (each n=20).The duration of study for each patient was 90 days(3 months). All the patients were from low socioeconomic group taking vegetarian diet. The dropout patients were replaced by new patients in the study.

Exclusion criteria: Pregnant women with Hb<7gm%, History of severe oral intolerance, Excessive emesis , Bleeding piles , Active peptic ulcer , high obstetric risk associated with hypertension, diabetes, hepatic and renal diseases and Other GIT problem were excluded from the study.

Medication: Study medication was supplied in the form of tablets.

Group A: Combination of ferrous fumarate containing 100mg elemental iron along with folic acid 1.5mg.Vit B1210mcg administered once a day.

Group B: Combination of ferrous bisglycinate containing 100mg elemental iron along with folic acid 1.5mg. Vit B1210 mcg administered once a day.

Group C: Combination of carbonyl iron containing 100mg elemental iron along with folic acid 1.5mg. Vit B1210 mcg administered once a day.

After recruitment, the patients were supplied with the respective medication and asked to follow-up after each month (30 days).During each follow-up visit, they were subjected to general and obstetric examination and supplied with study medication for the next 30 days. Compliance was checked by verbal enquiry and verified by checking empty or used packets of the drug brought by patients. Patients were also informed and given a reminder on phone for the date of next visit as well as adherence to the given medication was confirmed.

*Investigations:*Samples for blood investigation were collected at day 0(before starting medication), day 30(end of1stmonth), day60 (end of 2ndmonth) day90(end of 3rdmonth) The parameters of Hb, MCV, retic count were assessed at day 0, and then at the end of 1st,2nd,and 3rd month. Serum ferritin was assessed at recruitment (day 0) and at the end of 3rd month. The amount of blood collected at each visit was 4 to 5ml. Parameters like Hb and MCV were done on automatic cell counter (sysmax).Reticulocyte count was done by slide method and Serum ferritin was done by biochemistry analyzer.

Safety measures: Patients were trained to record and observe the adverse effects and instructed to report immediately if serious ADR occurs. Any adverse event like metallic taste, epigastric distress, abdominal pain, nausea, vomiting, diarrhea and constipation, were recorded on Case record form. Also during follow-up visit patients were evaluated for following symptoms associated with iron deficiency anaemia, fatigue, malaise, loss of appetite, breathlessness, palpitation, giddiness, irritability.

In all tests mean values of test groups (B and C) were compared with mean values of control group (A). ANOVA (one way) test was used to test the significance of difference in overall efficacy of all the three treatments in producing rise in Hb or change in other parameters. All data was analyzed by using ANOVA for between the group comparison. Paired‘t’ test used when only one pair was to be compared, .Chi-square test was used to analyze adverse drug reactions of patients in

all 3 groups. For all statistical tests a 'p' value<0.05 was considered as significant and 'p' value <0.001 was considered as highly signify-cant. A 'p' value >0.05 was considered as insignificant.

Results

The base line Hb level (before starting treatment) was measured in all groups. All the three groups showed significant rise in Hb level over the basal values of respective group (p<0.001) at the end of the treatment (after 3 months) (Table.1). After doing intergroup comparison no significant difference was found in efficacy of three drugs (p>0.05).

Table-1: Comparative haematocrit parameters in various groups

Haematocrit parameters	Day 0	Day 30	Day 60	Day 90
Hemoglobin (g /dl) mean ± SD				
A	8..96 ± 0.74	10.26 ± 0.69	10.78 ± 0.62	11.48 ± 0.89**
B	9.40 ± 0.55	10.34 ± 0.72	11.01 ± 0.60	11.59 ± 0,46**
C	8.87 ± 1.17	9. 92 ± 1.40	10.44 ± 1.30	11.10 ± 1.01**
Mean corpuscular volume (M.C.V)(fl)				
A	73.65 ± 3.19	74.84 ± 3.01	73.62 ± 3.23	75.52 ± 3.59
B	74.27 ± 11.72	75.64 ± 10.58	75.71 ± 10.21	75.76 ± 9.98
C	73.51 ± 6.20	75.57 ± 6.29	73.85 ± 5.40	76.68 ± 5.14
Reticulocyte Count (%)				
A	0.85 ± 0.29	1.36 ± 0.62	1.13 ± 0.40	1.58 ± 0.69**
B	1.15 ± 0.42	1.19 ± 0.28	1.53 ± 0.34	1.65 ± 0. 36**
C	1.20 ± 0.58	1.76 ± 0.98	1.43 ± 0.47	1.48 ± 0.46

** p < 0.001- highly significant
A (n=20 Ferrous fumarate) , B (n=20 Ferrous bisglycinate) , C (n=20 Carbonyl iron)

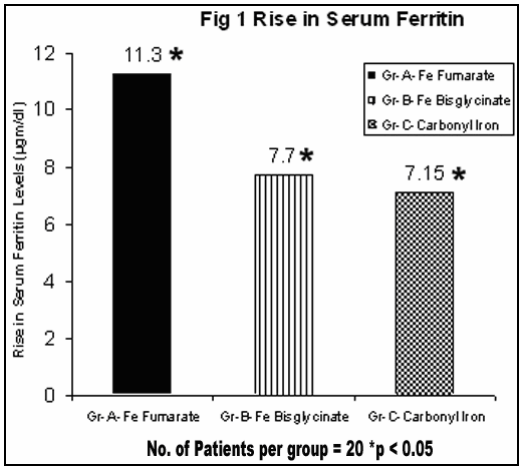
From Table 1 it is clearly seen that there is no significant increase in mean MCV value over the basal value with all the three groups at the end of three months (p>0.05).It is seen that (table 1) in group A and group B there is significant increase in mean retic count over the basal values at the end of three months (p<0.001). However in group C there is only borderline increase in retic count (p=0.065)

Table-2: Serum ferritin level before and after treatment(µg/ l)

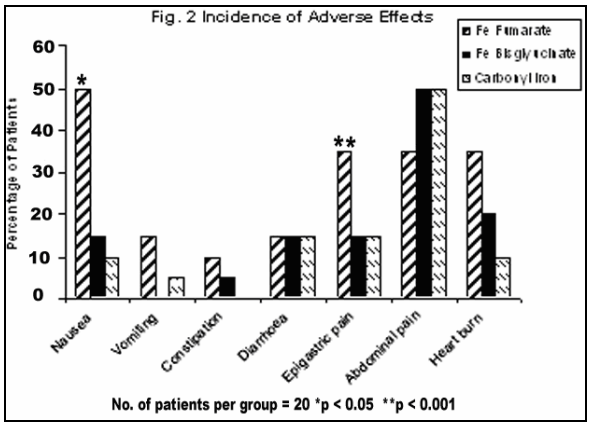
Serum Concentration	Day 0	Day 90
A	46.55 ± 34.55	57.85 ± 36.08*
B	29.30 ± 11.49	37.00 ± 12.15*
C	33.95 ± 21.05	41.10 ± 21.24*

* p < 0.05 – significant
A (n=20 Ferrous fumarate) , B (n=20Ferrous bisglycinate) , C (n=20 Carbonyl iron)

From table 2 in all the three groups there is significant increase in serum ferritin level (p<0.05),over the basal values. When all three groups are compared there is significant difference in serum ferritin at the end of three months(p<0.05). After doing intergroup comparison it was observed that increase in mean serum ferritin in group A was significantly higher (p<0.05), as compared to group B and C. Thus appreciable increase in iron stores are seen with group A (ferrous fumarate).



All patients were monitored for any adverse events in all follow-up visits. No patient was withdrawn from study due to ADRs. Overall the adverse effects were more common in group A. It was found that nausea ($p<0.05$) and epigastric pain ($p<0.001$) was significantly high with group A as compared with group B and C. There was no serious adverse events in any patient. There was no significant difference with other ADRs in all three groups.



We collected information of price of 5 brands of each iron salt studied from CIMS. The mean cost per tablet of each salt was compared with each other. From table 3 Fe Fumarate is the cheapest drug than other two drugs and Fe bisglycinate is the costliest drug.

Table-3: Comparison of cost of three drugs

Drug	Unit Cost	Cost per month (elemental iron)
Fe-fumarate (A)	₹ 1.14	₹ 34.20
Fe bisglycinate(B)	₹ 6. 20	₹ 186
Carbonyl iron(C)	₹ 3. 50	₹ 105

Discussion

As we know iron deficiency anaemia is very common world wide. In India, prevalence of anaemia in pregnancy is high. Pregnancy with anaemia has a significant impact on the health of fetus as well as that of the mother [3]. The treatment of IDA is given to replenish Hb and restore iron stores by supplying sufficient iron. Routine iron supplementation with iron salt show low efficacy for the control of IDA due to poor compliance with the treatment, because of its disagreeable flavor and adverse effects such as nausea, vomiting, constipation, diarrhea, abdominal pain [5]. Ideally a supplementation with a well accepted iron compounds accompanied with proper patient education could improve the compliance of iron supplementation resulting in significant reduction in prevalence of IDA.

Among the possible alternatives to control iron deficiency, iron bisglycinate chelate has been formulated in such a way that, it is a amino acid chelate. When glycine, forms a bisglycinate chelate, which is more stable has high bioavailability, ensures less GI irritation and absorption of bisglycinate is not affected by phytates in food [9]. There are different studies which shows bisglycinate has high bioavailability and good regulation. Bisglycinate chelate has been used and successfully evaluated in Brazil, for iron fortification. As a supplement it has been tested in other countries and has shown a great efficacy in reducing iron deficiency and IDA [10].

In a comparison study by Ashmead et al with ferrous sulfate and ferrous bisglycinate it is reported that both groups showed signify-cant increase in Hb level, but group with Fe bisglycinate had significant rise in plasma ferritin.This study was not done in pregnant women[7,10]. In other study which involved pregnant women with IDA demonstrating comparable efficacy of iron bisglycinate and Fe sulfate and found iron bisglycinate to be more effective than Fe sulfate with less adverse effects [4]. Other new iron salt Carbonyl iron, a pure form of elemental iron widely used as a food additive. As a supplement carbonyl iron is given as small particles (<5μ). It has slow and continuous absorption of iron with less side effects. VR Gordeuk and colleagues in their comparative study between carbonyl iron and Fe sulfate found carbonyl iron to be more effective and had less side effects than Fe sulfate [8,11]. Devasthali et al compared ferrous sulfate and carbonyl iron in healthy blood donors and found the overall bioavailability of carbonyl iron was 70% more than that of Fe sulfate [12].

In present study randomized single blind controlled trial involving pregnant anaemic women we found ferrous bisglycinate and carbonyl iron have equal efficacy with ferrous

fumarate in increasing serum Hb. Serum ferritin levels were more effectively increased with ferrous fumarate.This finding contradicts those reported by Ashmed and Szarfarc.Overall adverse effects were more common with ferrous fumarate, (but were not severe enough to warrant discontinuation of iron therapy) than with ferrous bisglycinate and carbonyl iron .Similar results were observed by Adsul BB et al[1] and Sophia Szarfarc [4]. None of the above studies compared cost effectiveness of all the three drugs. The pharmacoeconomic analysis shows that Fe fumarate is more cheap than other two drugs. Bisglycinate is most costly drug.

Conclusion

Thus considering all above parameters all three drugs are equally effective. Ferrous fumarate is cheap with tolerable adverse effects and it increases iron stores significantly. Ferrous bisglycinate and carbonyl iron show equal efficacy as Ferrous fumarate in increasing Hb and produced less adverse effects than ferrous fumarate, but are very costly. Thus Ferrous fumarate still can be considered as best cost effective choice with tolerable adverse effects for treatment as well as prevention of iron deficiency anaemia in pregnancy.

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*All correspondences to: Dr. Mrs S.S. Patil, 3,Celina Appartment ,New Palace Area, Kolhapur, Maharashtra**,** India.
E-mail: drpsunita@rediffmail.com