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Comparison of Various Oral Iron Salts in the Treatment of Iron Deficiency Anemia in Pregnancy

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ABSTRACT

Background: *To compare the efficacy and side effects of ferrous sulphate, fumarate, ascorbate, sodium feredetate and ferrous bisglycinate in the treatment of iron deficiency anemia in pregnancy.*

Material and methods: *The study is a prospective, randomized, comparative clinical study comprising of 250 antenatal women with hemoglobin between 7-10 gm %. The patients divided into five groups I, II,III,IV and IV of fifty each, by systematic randomization and were treated with ferrous sulphate (100mg), ferrous fumarate (100mg), ferrous ascorbate (100mg), ferrous bisglycinate (30 mg), sodium feredetate (33 mg) respectively. Hemoglobin estimation was done at day 0, 30 and 60 and serum ferritin levels were done on day 0 and 60.*

Results: *There was significant and comparable rise in hemoglobin on day 30 and day 60 in all the five groups ($p<0.001$). Ferrous ascorbate and ferrous bisglycinate showed significantly ($p<0.05$) more rise as compared to ferrous sulphate. Maximum side effects were with ferrous fumarate (51) followed by ferrous sulphate (40), ferrous bisgylycinate (26), ascorbate (18) and sodium feredetate (10).*

Conclusion: *Ferrous ascorbate and bisglycinate are more effective than ferrous sulphate in treatment of iron deficiency anemia in pregnancy. Sodium feredetate had minimum side effects.*

Keywords: *Ferrous ascorbate, Ferrous bisglycinate, Ferrous fumarate, Ferrous sulphate, Sodium feredetate, Anemia, Pregnancy*

INTRODUCTION

As per WHO anemia is defined as hemoglobin concentration less than 11gm % (1). It is responsible directly or indirectly for 40-60% of maternal deaths from cardiac failure, hemorrhage, infection and pre-eclampsia (2). It also increases perinatal mortality and morbidity rates consequent of preterm deliveries, intra-uterine growth restriction, low iron stores, iron deficiency anemia, cognitive and affective dysfunction in infant (3, 4,5).

Anemia has a varied incidence, etiology and degree of severity in different populations; being more prevalent in developing countries where it remains an important cause of maternal mortality (6,7). Common causes of anemia in pregnancy are iron deficiency, folic acid deficiency, vitamin B12 deficiency and other nutrient deficiencies, and hemoglobinopathies of which iron deficiency anemia is the commonest cause (8,9). Iron deficiency anemia affects approximately 15% of the world's population. In pregnancy, it affects 22% of pregnant women in industrialized countries and 52% in non-industrialized countries (10).

Many iron preparation are available for the treatment of iron deficiency anemia in pregnancy. Ferrous sulphate is the most widely used iron preparation throughout the world (11,12). Conventional iron salts are associated with various side effects like nausea, vomiting, abdominal pain, constipation, diarrhea, dyspepsia etc. Moreover, absorption from these preparations is reduced by various ingredients in the meal like phytates, polyphenols, calcium and tannins which oxidize the ferrous iron to ferric iron (13). 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.

The present study was planned to compare the efficacy and side effects of ferrous sulphate, ferrous fumarate, ferrous ascorbate, sodium feredetate and ferrous bisglycinate in treatment of iron deficiency anemia in pregnancy.

MATERIAL AND METHODS

The present study was a prospective, randomized, comparative clinical study comprising of 250 antenatal women, suffering from iron deficiency anemia attending the antenatal clinic at a tertiary care centre in India.

After taking the ethical clearance from the institutional committee, wWomen between 16–28 weeks of pregnancy with hemoglobin between 7–10 gm % were included in the study. The patients were randomly assigned to five groups of 50 patients each using systematic randomization method. Group I was

given ferrous sulphate (100 mg elemental iron), group II was given ferrous fumarate (100 mg iron), group III was given ferrous ascorbate (100 mg iron), group IV was given ferrous bisglycinate (30 mg iron), group V was given sodium feredetate (33 mg iron). The patients were followed every 30 days for the next 2 months. Hemoglobin estimation was done at day 0, 30 and 60 and serum ferritin levels were done on day 0 and 60. Side effects of iron like epigastric pain, nausea, vomiting, diarrhea and constipation were also recorded on follow up visits.

Women intolerant to iron derivatives, suffering from any bleeding disorder like bleeding piles or active peptic ulcer, women with antepartum hemorrhage and those who delivered within two months of starting iron therapy were excluded from the study.

Primary outcome measures were rise in hemoglobin and serum ferritin levels. Secondary outcome measure was side effects of the iron salts. Data was compiled and analyzed using various tests student t test, anova, chi square and turkey's HSD tests.

RESULTS

Results are as shown in table 1-5. The mean age in group I, II, III, IV and V was 22.58±2.64, 22.74±2.47, 22.4±2.33, 22.14±2.16 and 22.41±2.32 years respectively. Maximum number of cases in all groups belonged to rural population (68% in group I, 80% in group II, 78% in group III, 76% in group IV and 64% in group V). All the five groups were comparable in terms of age, parity and period of gestation (POG).

Mean hemoglobin at enrolment in group I, II, III, IV and V was 8.53±0.813, 8.84±0.84, 8.73±0.796, 8.82±0.92 and 8.91±0.92 gm % respectively. Maximum side effects were with ferrous fumarate followed by ferrous sulphate, ferrous bisglycinate, ascorbate and sodium feredetate (Table 4). Most common side effect in group I and II was constipation (24% and 32% of patients respectively), in group III was dyspepsia (20% of patients) and in group IV was diarrhoea (16% of patients). Patients in group V showed least side effects among which abdominal pain and constipation were common (4% of patients each).

Table 1- Showing mean Hb rise in different groups

Group (n-50 in each)	**Mean Rise in Hb on day 30(D0-d30) (gm %)**	**Mean Rise in Hb on day 60(D0-60) (gm %)**	**t test (Rise from D0-D30)**	**t test (Rise from D0-D60)**
Group I (Ferrous sulphate)	0.56±0.23	0.93±0.27	P<0.001(S)	P<0.001(S)
Group II (Ferrous fumarate)	0.61±0.22	1.06±0.28	P<0.001(S)	P<0.001(S)
Group III (Ferrous ascorbate)	0.63±0.23	1.13±0.35	P<0.001(S)	P<0.001(S)
Group IV (ferrous bisgly-cinate)	0.66±0.23	1.11±0.27	P<0.001(S)	P<0.001(S)
Group V (sodium feredetate)	0.67±0.22	1.09±0.31	P<0.001(S)	P<0.001(S)
ANOVA	1.870	3.418		
p value	.116(NS)	.010(S)		

Table 2: Intergroup comparison of mean Hb rise from day 0 to day 60

Group	**group**	**Mean rise at day 60 gm %**	**p value**
Group I (Ferrous sulphate)	Group II (Fumarate)	1.06±0.28	0.178
	Group III (Ascorbate)	**1.13±0.35**	**0.024**
	Group IV (Bisglycinate)	**1.11±0.27**	**0.014**
	Group V (Feredetate)	1.09±0.31	0.081
Group II (Ferrous Fumarate)	Group III (Ascorbate)	1.13±0.35	0.978
	Group IV (bisglycinate)	1.11±0.27	0.995
	Group V (Feredetate)	1.09±0.31	1.000
Group III (Ferrous Ascorbate)	Group IV (Bisglycinate)	1.11±0.27	1.000
	Group V (Feredetate)	1.09±0.31	1.000
Group IV (Ferrous bisglycinate)	Group V (Feredetate)	1.09±0.31	1.000

(Turkey's HSD test)

Table 3: Mean ferritin and rise in ferritin values

Group	Ferritin on D0 (ng/ml)	Ferritin on D60 (ng/ml)	Mean rise D0-D60 (ng/ml)	Paired t test p value
Group I (Ferrous sulphate)	28.58±13.57	40.58±14.31	12.19±5.01	p<0.001
Group II (Ferrous fumarate)	29.35±14.57	41.88±18.04	12.65±5.77	p<0.001
Group III (Ferrous ascorbate)	23.76±10.81	37.27±15.70	13.44±7.89	p<0.001
Group IV (ferrous bisglycinate)	25.19±12.95	38.46±16.02	13.47±7.03	p<0.001
Group V (sodium feredetate)	29.85±14.09	41.78±15.07	11.95±3.95	p<0.001
ANOVA	2.194	0.889	0.663	
p value	0.07(NS)	0.471(NS)	0.618(NS)	

Table 4: Distribution of cases according to number of side effects

Group	Patient with 1 S/E	Patient with 2 S/E	Patient with 3 S/E	Patient with 4 S/E	Total no of patients with S/E (%)	Total no of S/E
Group I (Ferrous sulphate)	2	5	8	1	16(32)	40
Group II (Ferrous fumarate)	3	5	10	2	20(40)	51
Group III (Ferrous ascorbate)	6	3	2	0	11(22)	18
Group IV (Ferrous bisglycinate)	3	7	3	0	13(26)	26
Group V (Sodium feredetate)	5	1	1	0	7(14)	10

(Side effect- S/E)

Table 5- Inter group comparison of side effects

Group	Group	χ^2 value	p value
Group I (Ferrous sulphate)	Group II (Fumarate)	0.694	0.405(NS)
	Group III (Ascorbate)	1.268	0.260(NS)
	Group IV (Bisglycinate)	0.437	0.509(NS)
	Group V (Feredetate)	**4.574**	**0.032(S)**
Group II (Ferrous Fumarate)	Group III (Ascorbate)	3.787	0.052(NS)
	Group IV (bisglycinate)	2.216	0.137(NS)
	Group V (Feredetate)	**8.574**	**0.003(S)**
Group III (Ferrous Ascorbate)	Group IV (Bisglycinate)	0.219	0.640(NS)
	Group V (Feredetate)	1.084	0.298(NS)
Group IV (Ferrous bisglycinate)	Group V (Feredetate)	2.250	0.134(NS)

DISCUSSION

Anemia in pregnancy is a condition of low circulating hemoglobin in which the hemoglobin concentration has fallen below a threshold lying at two standard deviations below the median of a healthy population of the same age, sex and stage of pregnancy(4).

The mean rise in hemoglobin on day 60 was 0.93±0.27 gm % in group 1, 1.06±0.28 gm % in group II, 1.13±0.35 gm % in group III, 1.11±0.27 gm %in group IV and 1.09±0.31 gm % in group V which was significant (p<0.001, Table-1). On intergroup comparison it was found that maximum rise in Hb on day 60 was with ferrous ascorbate and minimum rise was with ferrous sulphate. Ferrous ascorbate and ferrous bisglycinate showed significantly more rise in Hb as compared to ferrous sulphate. Sodium feredetate and ferrous fumarate also showed more rise as compared to ferrous sulphate but the difference was not significant (Table-2). Agarwal and Rathi, 2005 conducted a comparative study to compare the efficacy of ferrous ascorbate and carbonyl iron and showed that ferrous ascorbate resulted in significantly higher increase in hemoglobin as compared to carbonyl iron(14). Sarkate et al, 2007 conducted a study comparing

efficacy of sodium feredetate with ferrous fumarate in pregnant anemic women and showed that hemoglobin rise was more with sodium feredetate than ferrous fumarate as in the present study (15). The reason for effectiveness of such small doses of sodium feredetate is its high bioavailability in phytate rich diet (16, 17,18). Szarfarc et al in their study concluded that ferrous bisglycinate was significantly more effective than ferrous sulphate even in lower doses as in our study (19). Study conducted by Patil et al showed comparable rise in Hb with ferrous bisglycinate, ferrous fumarate and carbonyl iron (20). The present study also showed comparable rise in hemoglobin with ferrous bisglycinate and ferrous fumarate.

Serum ferritin reflects body iron stores and increases with iron therapy. There was a significant rise in serum ferritin on day 60 in all the groups but the intergroup variation in rise in serum ferritin was not significant ($p>0.05$, Table 3). Pineda et al showed significant rise in serum ferritin with 60 mg and 120 mg of iron from ferrous bisglycinate and with 120 mg of iron from ferrous sulphate and not with ferrous bisglycinate containing 30 mg of iron (21). In the present study however, ferrous bisglycinate containing 30 mg of iron also showed significant rise in serum ferritin at the end of study. Sarkate et al also comparable rise in serum ferritin with 33 mg iron from sodium feredetate and 100 mg of iron from ferrous fumarate as in our study (15).

Maximum side effects were with ferrous fumarate followed by ferrous sulphate. Minimum side effects were with sodium feredetate (Table 4). The side effects reported by women were tolerable and not to the extent of leading to discontinuation of iron salts. Melamed et al conducted a study to assess the use, side effects and discontinuation rates of iron preparations in pregnancy. They found that maximum side effects were with ferrous fumarate and minimum with ferrous bisglycinate (22). But in the present study, side effects of ferrous bisglycinate were comparable to ferrous fumarate and ferrous sulphate.

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