Research Analysis Report

A Randomised Double-blind Study Comparing Sodium Feredetate with Ferrous Fumarate in Anaemia in Pregnancy

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Iron deficiency anaemia is a major health problem in India especially in women of reproductive age group. The World Health Organisation recommends that the haemoglobin concentration should not fall below 11.0 g/dl at any time during pregnancy. The aim of study was to compare the efficacy and safety of two doses of sodium feredetate with ferrous fumarate in improving haemoglobin profile in pregnant anaemic women. Pregnant women with gestation period between 12 and 26 weeks having serum haemoglobin <10 g/dl, serum ferritin levels less than 12 μg/l were included in the study. Patients were divided into 3 groups and drugs administered accordingly. A total of 48 patients were available for analysis which included 37 patients who had completed all the visits up to 75 days follow-up and 11 patients who were treatment failures. In group A combination of sodium feredetate (containing 33 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) was administered twice a day. In group B combination of sodium feredetate (containing 66 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) was administered twice a day. In group C combination of ferrous fumarate (containing 100 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) was administered twice a day. Patients were evaluated for Hb, RBC count, MCV, MCH and MCHC at day 0, 30, 45, 60 and 75. Serum ferritin, serum iron, TIBC and transferrin saturation were assessed at recruitment and end study. Mean rise of haemoglobin at the completion of study, over that of basal values was 1.79g/dl (0.71 to 2.87, 95% CI, p<0.05) in group A, 1.84g/dl (0.82 to 2.86, 95% CI, p<0.05) in group B and 1.63g/dl (0.38 to 2.88, 95% CI, p<0.05) in group C. Safety assessment was done by doing liver and kidney function test at the time of recruitment and end study. Low doses of sodium feredetate (33mg and 66mg of elemental iron given twice daily) produce comparable results as higher dose of ferrous fumarate (100mg elemental iron given twice daily). As there were no adverse effects reported with sodium feredetate, it can be concluded from this study that this new formulation appears to be effective in improving haemoglobin profile in pregnant anaemic women and is tolerated well. [*J Indian Med Assoc* 2007; **105**: 278-81 & 284]

Key words **: Iron deficiency anaemia, haemoglobin, pregnant woman, sodium fereditate, ferrous fumarate.**

Iron deficiency anaemia is a major health problem worldwide. Especially in women of reproductive age group, there is a prevalence of anaemia and factors like malnutrition, blood loss during menstruation and delivery and depletion of stores during pregnancy and nursing period contribute to its development. The World Health Organisation recommends that the haemoglobin concentration should not fall below 11.0 g/dl at any time during pregnancy. Estimates from the World Health Organisation report that from 35% to 75% (56% on average) of pregnant women in developing countries, and 18% of women from industrialised countries are anaemic[1]. Iron deficiency anaemia is a major public health problem in India mostly affecting the pregnant women and young children. The estimated Indian prevalence of anaemia among pregnant women is 49.7%[2]. Iron salts like ferrous sulphate, fumarate or gluconate have been extensively used for the prevention and treatment of iron deficiency. Oral iron supplements, which are usually in the form of ferrous (Fe^{2+}) salts, are toxic to the gastro-intestinal mucosa, and so intolerance is common, resulting in poor compliance and failure of treatment[3]. To make iron more absorbable, reduce the side-effects of gastro-intestinal tract and at the same time not increase the harmful effects, newer and newer formulations are being brought in the market. Ferrous fumarate is one of the commonly used salts of iron in clinical practice. Sodium iron EDTA is water-soluble and highly bioavailable form of iron. The mean iron absorption of iron EDTA is considered to be approximately 3 times higher than from ferrous sulfate and is affected only slightly by the presence of inhibiting substances in diet[1]. Hence a double-blind, parallel group, randomised, controlled clinical study was planned in pregnant women to compare the efficacy and safety of the sodium iron EDTA with ferrous fumarate. The aim of our study was to compare the efficacy and safety of two doses of sodium feredetate with ferrous fumarate in improving haemoglobin profile in pregnant anaemic women.

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MATERIAL AND METHOD

It was intended that 45 pregnant women with gestation period between 12 and 26 weeks having serum Hb level <10 g/dl, serum ferritin levels <12 μg/l that consented for follow-up every 15 days regularly for 3 months be included in the study. However considering the drop-outs and treatment failure more patients were screened and finally a data of 48 patients were available.

Their peripheral smear showed hypochromic, microcytic/macrocytic RBCs. Exclusion criteria included haemoglobin below 7 g/dl; severe concurrent illness (cardiovascular, renal, hepatic or any other systemic diseases); history of chronic inflammation (rheumatoid arthritic, gout, etc); patients with bleeding piles, active peptic ulcer/oesophageal varices, history of drug intake (NSAIDs / steroids); known hypersensitivity to iron preparations; malignancy of any type or any other source of blood loss. Ethics Committee of Seth GS Medical College and KEM Hospital approved the protocol, and all patients gave informed written consent. After taking informed consent, the subjects were randomly enrolled to one of the three groups as per the computer generated randomised chart. The duration of study for each patient was 75 days.

Medication — Study medication was supplied in the form of

capsules in sealed plastic bottles supplied by Alkem Laboratories Limited.

Treatment groups — Group A : Combination of sodium feredetate (containing 33 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) administered twice a day.

Group B : Combination of sodium feredetate (containing 66 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) administered twice a day.

Group C : Combination of ferrous fumarate (containing 100 mg of elemental iron) along with vitamin B12 (15μg) and folic acid (1.5mg) administered twice a day.

After recruitment, the patients were supplied the respective study medication and asked to follow-up after every 15 days. During each follow-up visits, they were subjected to general and obstetric physical examination and supplied with study medications for the next 15 days. They were also screened for any adverse events suffered. Samples for the blood investigations were collected at days 30, 45, 60 and 75. The parameters of haemoglobin, RBC count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were assessed at day 0, day 30 and thereafter every 15 days till end of study (day 75). Serum ferritin, serum iron, total iron binding capacity (TIBC) and transferrin saturation were assessed at recruitment and end study. Safety assessment was done by doing liver and kidney function test at the time of recruitment and end study, and monitoring total and differential leucocyte count at the time of recruitment, at day 30 and thereafter every 15 days till end study. The amount of blood collected at the time of recruitment and end study was 7 ml and during other follow-up visits was 2 ml.

During all the follow-up visits, patients were evaluated for the following symptoms associated with iron deficiency anaemia: Fatigue, malaise, loss of appetite, breathlessness, palpitation, giddiness, irritability and reduced work performance. The scoring of each of these symptoms was done as nil: no occurrence of symptoms (1); mild: symptom present but not troublesome (2); moderate: annoying and disturbing daily activities (3); severe: continuously present, interferes with daily activities (4). For each patient, the scores for each of the symptoms were added to get a composite score of physical well-being. Thus, the maximum possible score was 23 and minimum score was 0. Smaller the score better was the physical health of the patient and vice versa.

Patients who were not responding to drug therapy with the treatment in either group (no rise in the haemoglobin by at least 1 g/dl even after one and half months of drug therapy) were considered as treatment failure. They were removed from the trial and their further treatment was decided by the obstetrician.

Statistical analysis — Statistical analysis was done using SPSS for windows (version 13.0) for all the analyses, except Friedman's test followed by Tukey's honestly significant difference (HSD) as post-hoc, which was done by primer of biostatistics (version 5.0). As some patients of each group were withdrawn from the trial at day 45 due to treatment failure, the data for their subsequent follow-up visits was computed by using the principle of last observation carry forward (LOCF) ie, the last reading available for such patient was carried forward in all the follow-up visits till the end of study.

Before analysis, each of the quantitative parameters was tested for normal distribution of the data by using one sample Kolmogorov-Smirnov test. If the basal values were found to be normally distributed, analysis was done using parametric tests. On the other hand, if the data was not normally distributed, then non-parametric tests were used. All the variables with ordinate data (based on ranks) were analysed by non-parametric tests.

Parametric tests — As the study design contained three different groups of patients on different treatments observed at repeated time intervals, split-plot repeated measures ANOVA test was used to test for significant difference in overall efficacy of all the three treatments in producing rise in haemoglobin or change in other parameters. All the parametric data was analysed by using one way ANOVA for between the groups comparison. If the significance is obtained, then multiple comparisons were done by Tukey's HSD test. The parameters of each individual group which were assessed at multiple points over a period of time, were analysed by using repeated measures ANOVA, followed by Bonferroni's t test (Tukey's HSD for repeated measures being not available in SPSS) for multiple comparisons or paired 't' test when only one pair was to be compared.

Non-parametric tests — Non-parametric data for between the groups comparison was analysed by Kruskal-Wallis test followed by Tukey's HSD test as a post hoc. For repeated measures, Freidman's statistic was used for testing the significance followed by Tukey's HSD test as post hoc.

Table 1 — *Age and Weight of Cases in Various Groups*

Group	Age in years		Weight in kg
	Mean ± SD	Range	(mean ± SD)
A	23.75 ± 2.96	20-20	46.06 ± 4.93
B	24.44 ± 3.86^{NS}	19-32	46.97^{NS} ± 7.55
C	24.19 ± 3.17^{NS}	20-30	46.25^{NS} ± 7.41

^{NS}Not significant *versus* group A using one way ANOVA followed by Tukey's HSD test

Chi-square test was used to analyse number of patients in all the three groups who failed to respond to the treatment after 45 days of medication. A two tailed p-value of <0.05 was considered significant in all the statistical tests.

Observations

A total of 48 patients were available for analysis which included 37 patients who had completed all the visits up to 75 days follow-up and 11 patients who were treatment failures. Baseline characteristics of patients included in the study are shown in Table 1.

Efficacy analysis — Low doses of sodium feredetate (33 mg and 66 mg of elemental iron given twice daily) produces comparable results in producing rise in haemoglobin as higher dose of ferrous fumarate (100mg elemental iron given twice daily).

All the three groups showed statistically significant rise of haemoglobin over the basal values as early as at day 30 itself. The subsequent observations ie, days 45, 60 and 75 showed continued rise of haemoglobin, with significant difference from the basal values. Mean rise of haemoglobin at the completion of study (day 75), over that of basal values was 1.79g/dl (0.71 to 2.87, 95% CI, p<0.05) in group A, 1.84g/dl (0.82 to 2.86, 95% CI, p<0.05) in group B and 1.63g/dl (0.38 to 2.88, 95% CI, p<0.05) in group C (Fig 1 & Table 2). Thus low doses of sodium feredetate (33mg and 66mg of elemental iron given twice daily)

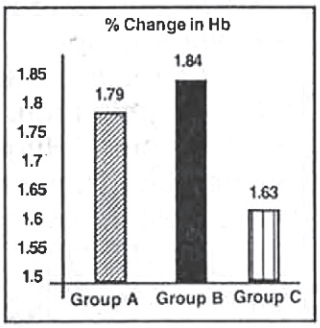

Fig 1 — Per Cent Change in Hb

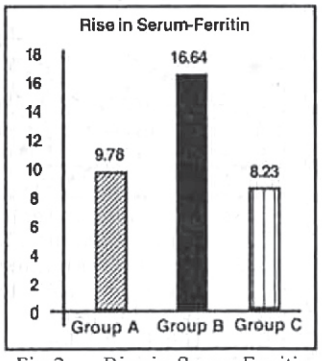

Fig 2 — Rise in Serum Ferritin in ng/ml

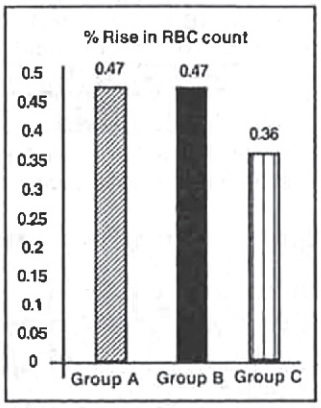

Fig 3 — Per Cent Rise in RBC Count

Table 2 — *Comparative Haematocrit Parameters in Various Groups*

Haematorcit parameters	Day 0	Day 30	Day 45	Day 60	Day 75
Haemoglobin (g/dl) (mean ± SD) :					
A	8.93 ±0.64	10.03* * * ±0.78	10.11*** ±0.61	10.41* * * *±0.75	10.72***# ±0.85
B	9.03NS ±0.71	10.42* * * *±0.56	10.62 NS * * * *±0.65	10.34* * * *±0.77	10.87 NS * * * NSI ±0.89
C	9.17NS ±0.85	10.16* * * ±1.19	10.34 NS* * * ±1.22	10.69* * * *±1.41	10.80 NS * * * NSI ±1.41
RBC count (million/cmm) :					
A	3.74 ±0.50	3.93NSI ±0.38	4.02NSI ±0.41	4.17* * ±0.51	4.2* * ±0.52
B	3.73NS ±0.52	4.05* ±0.56	4.09NS* ±0.45	4.01NSI ±0.42	4.20NS * * * ±0.415
C	3.93NS ±0.60	4.14NSI ±0.57	4.18NS NSI ±0.56	4.27NSI ±0.54	4.29NS NSI ±0.63
MCV (fl) :					
A	70.69 ±9.52	73.69NSI ±13.58	75.94NSI ±10.27	74.94NSI ±8.68	76.75NSI ±5.88
B	70.69NS ±13.61	72.56NSI ±11.01	76.31NS NSI ±9.21	74.88NSI ±7.03	75.25NS NSI ±9.11
C	69.19NS ±10.95	73.38NSI ±10.92	70.31NS NSI ±8.81	73.00NSI ±10.29	72.69NS NSI ±9.43
MCH (pg) :					
A	24.32 ±3.77	25.74* ±3.39	25.41NSI ±3.02	25.29NSI ±3.15	25.74 NSI ±2.80
B	24.68NS ±4.57	26.23* ±4.19	26.24NS NSI ±3.01	26.09NSI ±3.53	26.09NS NSI ±2.96
C	23.69NS ±3.41	24.81NSI ±3.32	25.00NS NSI ±3.59	25.24* ±3.36	25.43NS NSI ±3.66
MCHC (g%) :					
A	34.32 ±2.93	34.44NSI ±3.90	33.73NSI ±3.45	33.84NSI ±3.18	33.55NSI ±2.65
B	34.06NS ±3.55	36.35NSI ±4.26	34.58NS NSI ±3.92	34.80NSI ±3.01	34.83NS NSI ±2.77
C	34.48NS ±4.52	33.99NSI ±2.66	35.57NS NSI ±2.39	34.39NSI ±2.13	35.01NS NSI ±2.82

NSNot significant *versus* group A, using one way ANOVA followed by Tukey's HSD test
NSINot significant *versus* day 0, using repeated measures ANOVA followed by Bonferroni's 't' test
*p<0.05 *versus* day 0, using repeated measures ANOVA followed by Bonferroni's 't' test
**p<0.01 *versus* day 0, using repeated measures ANOVA followed by Bonferroni's 't' test
***p<0.001 *versus* day 0, using repeated measures ANOVA followed by Bonferroni's 't' test

produced more rise in haemoglobin as compared to higher dose of ferrous fumarate (100mg elemental iron given twice daily).

Proportion of treatment failures ie, haemoglobin rise of less than 1 g/dl at the end of 45 days of treatment, was 18.75% for group A, 25% for group B and 25% for group C.

Mean rise of ferritin levels at the completion of study (day 75), over that of basal values was 9.78 ng/ml (-1.87 to 21.44, 95% CI, p<0.05) in group A, 16.64 ng/ml (-8.64 to 41.91, 95% CI, p<0.05) in group B and 8.23 ng/ml (2.29 to 14.16, 95% CI, p<0.05) in group C (Fig 2 and Table 3). Thus, this study indicates that the sodium feredetate 66mg twice daily is more effective in increasing the serum ferritin level, than the sodium feredetate 33mg twice daily or ferrous fumarate 100mg twice daily.

All the three groups showed rise of RBC count over the basal values at day 75. However, this increase in RBC count was not statistically significant in group C. Mean rise in RBC count at the completion of study (day 75), over that of basal values was 0.47 millions/cmm (0.13 to 0.80, 95% CI, p<0.05) in group A, 0.47 million/cmm (0.16 to 0.77, 95% CI, p<0.05) in group B and 0.36 million/cmm (-0.05 to 0.78, 95% CI, p<0.05) in group C (Fig 3 and Table 2). All the three groups showed a rise in MCV over the basal values at day 75 (Table 2).

Composite score of physical well-being — In all the three treatment groups, the composite score of physical well-being improved (decreased) at day 15 itself, with statistically significant difference from the basal score (Table 4).

Compliance and safety evaluation — All the patients were monitored for any adverse events in all the follow-up visits. They were specifically asked for diarrhoea, constipation, gastro-intestinal irritation or any other side-effects. None of the patients in any of the treatment groups reported any side-effects. Also there were no side effects reported in any of the drop-out patients during their completed follow-ups. There were no incidences of any serious adverse event.

Discussion

Above results show that when administered with same doses of vitamin B12 and folic acid, sodium feredetate 33mg twice daily and 66mg twice daily were as effective as ferrous fumarate (100mg) twice daily in increasing the haemoglobin of pregnant women with iron deficiency anaemia. All the three treatments caused significant increase in the haemoglobin values after one month of treatment. Also, there was continued rise of haemoglobin with further treatment. Although this increase of haemoglobin did not achieve any statistically significant difference from day 30 values, it is important from the clinician's point of view, as it brought most of the patients into the normal range of haemoglobin at day 75. The number of treatment failures at day 45 in all the three groups were comparable. All the three treatments were found to have significantly increased serum ferritin levels after 75 days of therapy, and thus were helpful in building the body stores of iron. All the patients showed a significant rise in serum ferritin at the end of 75 days indicating a rise in depleted iron stores. However, only two patients in each of the three groups had final serum ferritin levels in the normal range. This is expected as the body and tissue stores of iron start increasing only with continued treatment after the correction of anaemia. The mean rise in serum ferritin was quantitatively more with sodium feredetate, especially with 66mg dose.

Values of serum iron, TIBC and TS are not sensitive tests for the diagnosis of iron deficiency anaemia, as these parameters can be in the

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longitudinal study. *J Gerontol* 1976; **31:** 155-63.

5 Halter JB — Principles of Geriatric Medicine. New York: McGraw-Hill, 1985: 218-30.

6 Beers MH — Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. *Arch Intern Med* 1997; **157:** 1531-6.

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Table 3 — *Comparative Values of Various Serum Constituents before and after Treatment*

Blood constituent	Group A		Group B		Group C	
	Basal (day 0)	Final (day 75)	Basal (day 0)	Final (day 75)	Basal (day 0)	Final (day 75)
Serum ferritin (ng/ml)	6.44 ±3.21	16.22* ±19.89	6.60^{NS} ±3.36	23.24^{NS*} ±38.48	5.95^{NS} ±3.0	14.18^{NS*} ±8.23
Serum iron (µg/dl)	76.43 ±19.11	116.8* ± 103.44	83.04^{NS} ± 30.08	114.16^{NS*} ±31.59	73.56^{NS} ±39.83	118.26^{NS*} *±59.84
TIBC (µg/dl)	287.83 ±43.85	326.26^{NS†} ±71.32	288.57^{NS} ±43.97	323.28$^{NS\ NS\dagger}$ ±86.61	279.90^{NS} ±63.48	287.68$^{NS\ NS\dagger}$ ±97.71
TS (%)	26.85 ±6.30	34.05^{NS†} ±21.69	28.77^{NS} ±8.94	37.07$^{NS\ NS\dagger}$ ±11.49	28.68^{NS} ±21.10	44.33^{NS*} ±21.30

TIBC: Total iron binding capacity; TS: Transferrin saturation

^{NS}Not significant *versus* group A, using one way ANOVA followed by Tukey's HSD test

*p<0.05 *versus* day 0, using paired 't' test (statistical significance for group A and B was obtained after removing the outliers)

**p<0.01 *versus* day 0, using paired 't' test

^{NS†}Not significant *versus* day 0, using paired 't' test

^{NS†}Not significant *versus* day 0, using paired 't' test

Table 4 — *Comparative Values of Mean Score of Well-being*

Group	Mean composite score					
	Day 0	Day 15	Day 30	Day 45	Day 60	Day 75
A	4.31	2.31*	1.25*	0.81*	0.81*	0.44*#
B	4.31^{NS}	2.56*	1.38*	0.75^{NS}*	0.94*	0.56^{NS}*#
C	4.31^{NS}	2.94*	1.88*	1.00^{NS}*	0.63*	0.44^{NS}*#

^{NS}Not significant *versus* group A, using Kruskal-Wallis test followed by Tukey's HSD test

*p<0.05 *versus* day 0, using Freidman's test followed by Tukey's HSD test

#p<0.05 *versus* day 45, using Freidman's test followed by Tukey's HSD test

normal range in mild anaemia[5]. RBC counts were increased in all the three treatment groups, due to better haematopoiesis. This increase in the RBC count was statistically significant at day 30 itself, with sodium feredetate 66mg dose. All the subsequent observations showed statistically significant difference from basal values. Sodium feredetate 33mg dose produced statistically significant increase in RBC count after 60 days of therapy. Though there was increase in the RBC count with ferrous fumarate as well, this was not statistically significant. There was no significant change in the mean MCHC. This is because, although there is increase in the absolute quantity of haemoglobin (MCH) in each RBC, this is compensated by the increase in the size (MCV) of RBC. Thus, the intracellular concentration of haemoglobin (MCHC) remains more or less constant or at most, increases only modestly.

Sodium feredetate either in 33 mg (of elemental iron) twice daily dose or 66 mg (of elemental iron) twice daily dose is as effective as ferrous fumarate 100 mg (of elemental iron) twice daily, in increasing the haemoglobin in patients of iron deficiency anaemia in pregnancy. As there were no adverse effects reported with sodium feredetate, we can conclude from this study that this new formulation appears to be effective in improving haemoglobin profile in pregnant anaemic women and is tolerated well. Also, two low doses of sodium feredetate (33mg and 66mg of elemental iron given twice daily) produces comparable results as higher dose of ferrous fumarate (100mg elemental iron given twice daily).

ACKNOWLEDGMENT

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REFERENCES

1 Allen LH — Anemia and iron deficiency: effects on pregnancy outcome1–3. *Am J Clin Nutr* 2000; **71:** 1280S–4S.

2 National Family Health Survey-II (NFHS-II) Delhi — Anaemia among Women and Children. Mumbai. International Institute for Population Sciences, 2002: 141-57.

3 Harvey RSJ, Reffitt DM, Doig LA, Meenan J, Ellis RD, Thompson RPH, *et al* — Ferric trimaltol corrects iron deficiency anaemia in patients intolerant of iron. *Aliment Pharmacol Ther* 1998; **12:** 845-8.

4 Mendoza C, Viteri FE, Lönnerdal B, Raboy V, Young KA, Brown KH — Absorption of iron from unmodified maize and genetically altered, low-phytate maize fortified with ferrous sulfate or sodium iron EDTA. *Am J Clin Nutr* 2001; **73:** 80–5.

5 Peter F, Wang S — Serum iron and total iron-binding capacity compared with serum ferritin in assessment of iron deficiency. *Clin Chem* 1981; **27:** 276-9.