An evaluation of sodium feredetate (NaFeEDTA) for the treatment of iron deficiency anaemia in Indian patients

Aim: The study was conducted to evaluate the efficacy of sodium feredetate in pregnant women with iron deficiency anaemia.

Design: Thirty pregnant women with iron deficiency anaemia who came for routine antenatal checkups in the Out-Patient Department of Safdarjang Hospital, New Delhi, were given sodium feredetate tablets (elemental iron 33mg) orally, once a day for a period of one month. Patients already taking some other iron supplementation or having any other high risk factor or having multiple pregnancies were excluded from the study. Patients were assessed for haemoglobin (Hb), serum iron (Serum Fe), total iron binding capacity (TIBC), and serum sodium (Serum Na) concentrations.

Results: Eight patients dropped out of the study group, as they did not report for the subsequent checkups. After one month of treatment, there was a significant increase in Hb level and serum Fe concentration in rest of the 22 patients. Haemoglobin levels increased from 8.75 ± 1.24g/dL to 10.53 ± 1.63g/dL (p value < 0.05). Similar rise in serum Fe from 28.33 ± 4.44 to 35.10 ± 3.42 µg/dL (p value < 0.05) and fall in TIBC from 460.72 ± 57.37 to 380.22 ± 66.87 µg/dL (p value < 0.05) was observed. No patient during and after the treatment showed significant change in blood pressure (p value < 0.42) and concentration of serum sodium (p value < 0.21). No serious side-effects were seen.

Conclusion: It was concluded that intervention with sodium feredetate (NaFeEDTA) led to a significant rise in haemoglobin levels in the treatment group, no significant side-effects were observed. Sodium feredetate was found to be efficacious in improving iron status in anaemic pregnant women and hence is a promising haematinic for patients with iron-deficiency anaemia.

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Introduction

Iron deficiency anaemia (IDA) is the most common type of anaemia affecting more than a billion people worldwide. In developing countries, there is a high prevalence of iron deficiency anaemia and to a lesser extent, in the more industrialised countries of the world.[1] Most critically affected are infants, school age children and women of reproductive age especially pregnant women.[1]

The major causative factor for IDA in developing countries is generally low iron absorption rather than low iron intake. Iron intake is

often relatively high, almost 20mg/day and would easily meet the recommended dietary allowances. However, much of the ingested iron is poorly bioavailable iron from plant sources or is contamination iron from soil and includes little bioavailable iron from animal tissues, so that high prevalence of iron deficiency and anaemia often co-exist with adequate total iron intakes. Cereals and legumes, which form a major part of the staple diet contain high levels of phytic acid, which is a potent inhibitor of iron absorption[2,3] and some such as sorghum also contain phenolic compounds which greatly impede iron absorption.

Food components such as phytates, tannins, and selected dietary fibres, which bind with iron, in the intestinal lumen, can impair iron absorption. Phytate is the component that probably has the greatest effect on iron status because many plant foods have high phytate contents that can severely impair iron absorption. Phytates constitute about 1 to 2 percent of the weight of many cereals, nuts, seeds and legumes. They prevent the accumulation of excessively large amounts of inorganic phosphorus during seed maturation by acting as a phosphorus store. About 75 percent of phytic acid is associated with soluble fibre components of foods.[4] The majority of *in vivo* studies show that phytates inhibit dietary iron bioavailability probably due to the formation of di-and tetra-ferric phytates from which iron absorption is poor.[4,5,6] In fact, the consensus among various studies and reviews is that the high phytate content of most plant staples is the primary cause of inhibition of iron absorption from plant-based diets.[4,5,6]

The key to the long-term prevention of iron deficiency and resulting anaemia is to increase the amount of bioavailability of dietary iron. The most commonly used strategies to combat iron deficiency are the provision of iron supplements which are unaffected by the staple phytate-rich diet.

Iron deficiency anaemia is a major nutritional problem especially in populations where iron requirement is high e.g., during pregnancy, as it has a direct impact on the growing foetus and the iron-stores of the infant in the long run.

Aim

The aim of this study was to evaluate the effectiveness of sodium feredetate in raising the haemoglobin levels of pregnant women with iron deficiency anaemia and to look for any adverse side-effects.

Materials and methods

The study was carried out on pregnant women with iron deficiency anaemia attending antenatal OPD at Safdarjang Hospital (all patients were of low/middle socio-economic group). According to the diagnostic criteria of anaemia recommended by WHO, pregnant patients with haemoglobin (Hb) value <11g/dL were taken for the study.

The patients recruited for the study were 17-28 years old and had haemoglobin concentration of >6g/dL but <11g/dL in the initial haemoglobin screening. Patients already taking some other iron supplementation or having any other high risk factor or having multiple pregnancies were excluded from the study. All women were informed verbally about the aim and the procedures of the study and a written informed consent was obtained from all of them before enrolling them in the study. Brief history was taken and patients were subjected to clinical examination. Blood sample of the treatment group were collected at baseline (t_0), at 2 weeks (t_2) and after 4 weeks (t_4), to determine haemoglobin (Hb), serum iron (serum Fe), total iron binding capacity (TIBC) and serum sodium (serum Na) levels.

Iron deficiency is defined as low haemoglobin concentration or low serum iron concentration or an elevated total iron binding concentration.

Haemoglobin level estimation was done by Cyanmeth method (by modified Drabkin solution) and serum Fe and TIBC were done by Ferrozine method. Serum electrolyte estimation was done by ion selective electrode (ISE) method. Patients were then given one tablet each of sodium feredetate (containing 33mg elemental iron) orally, once a day.

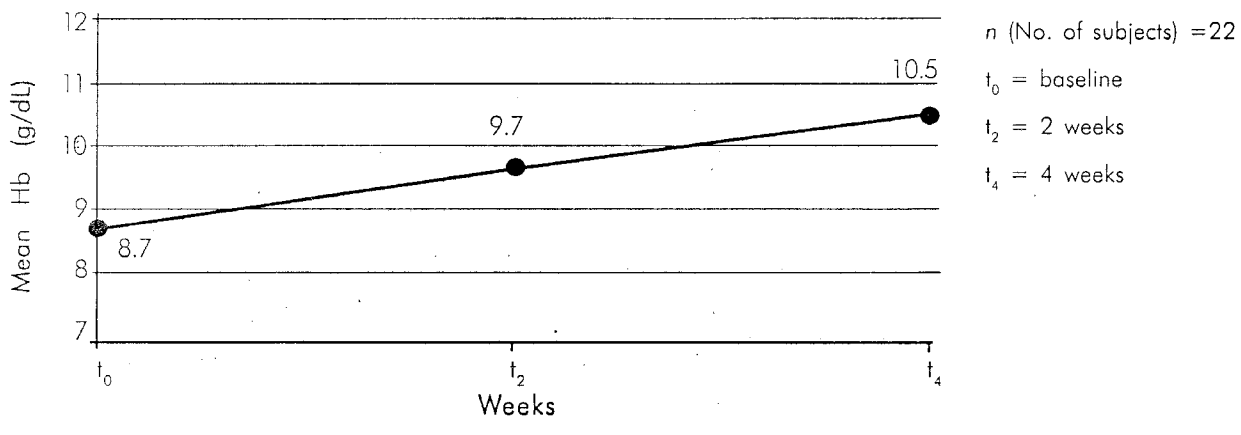

Fig. 1: Mean haemoglobin (g/dL) level in 22 subjects before and after the treatment with 33mg elemental iron per person per day as sodium feredetate

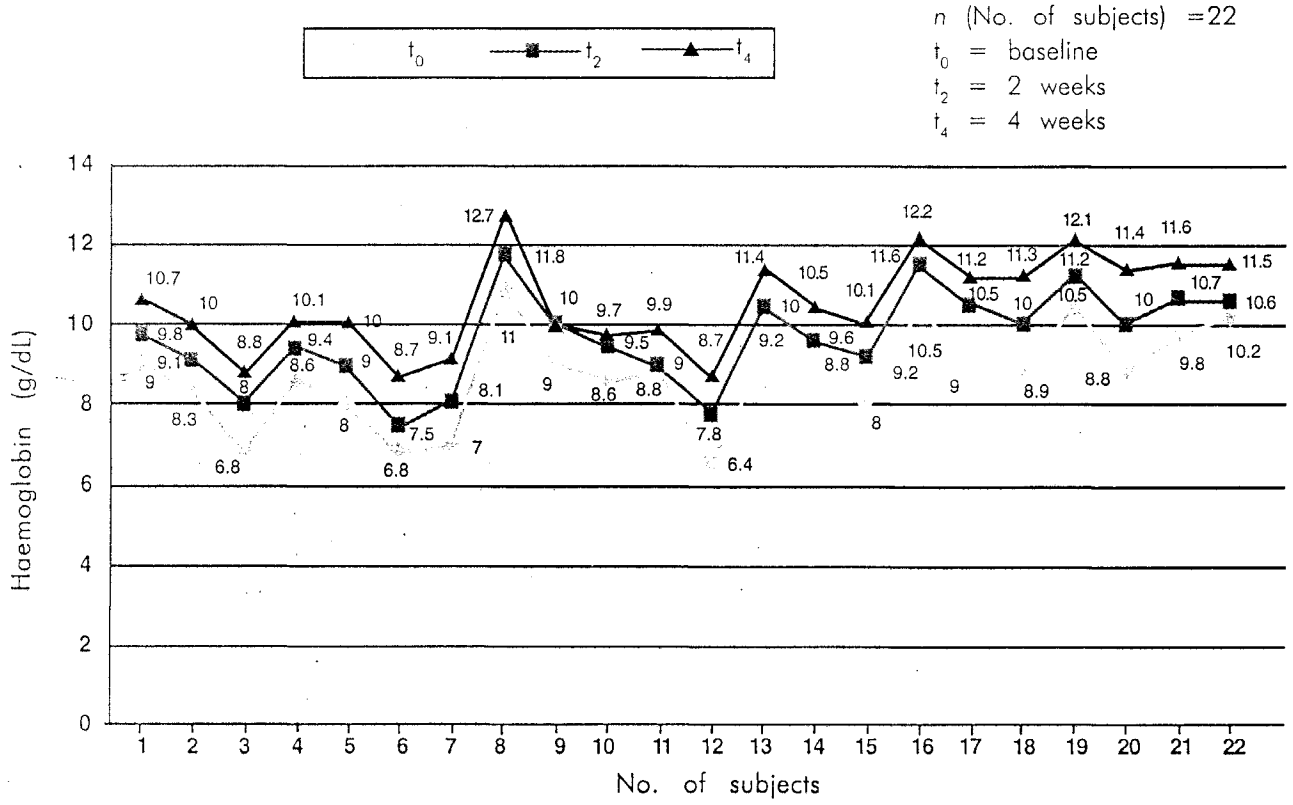

Fig. 2: Rise in haemoglobin (g/dL) levels in all the 22 subjects before and after treatment with 33mg elemental iron per person per day as sodium feredetate

At subsequent visits compliance was noted, blood pressure was recorded, blood samples were collected and patients questioned for any adverse gastrointestinal disturbances like nausea, vomiting, constipation or diarrhoea.

Results

Twenty two pregnant women with haemoglobin <11g/dL were studied. Mean haemoglobin of these anaemic women was 8.72 ± 1.241g/dL before intervention. The mean increase in Hb values after 4 weeks of treatment was 1.8g/dL. There was a significant increase in haemoglobin (Hb) levels after 4 weeks of treatment with sodium feredetate (Mean 10.53 ± 1.63 g/dL with $p < 0.05$) in the study group (Figs. 1 and 2). Serum iron concentration also showed a significant increase of 6.8 µg/dL ($p < 0.05$), in the treatment group after 4 weeks of intervention (Table 1).

Table 1 also shows significant decrease of 80.5µg/dL ($p < 0.05$) in the total iron binding capacity (TIBC) after treatment with sodium feredetate.

Table 2 shows that there is no significant rise in serum sodium levels in patients on treatment with sodium feredetate. No significant

Table 1: Effect of sodium feredetate on haemoglobin, serum iron and total iron binding capacity

Indicators	Before treatment (t_0)	After treatment (t_4)	p value	Remarks
Hb (g/dL)	8.75 ± 1.24	10.53 ± 1.63	$p < 0.05$	Significant
Serum Fe (µg/dL)	28.33 ± 4.44	35.10 ± 3.42	$p < 0.05$	Significant
TIBC (µg/dL)	460.72 ± 57.37	380.22 ± 66.87	$p < 0.05$	Significant

Table 2: Effect of sodium feredetate on serum sodium and blood pressure

Indicators	Before treatment (t_0)	After treatment (t_4)	p value	Remarks
Serum Na (µg/dL)	140.96 ± 2.19	142.25 ± 1.71	$p < 0.21$	Not Significant
Blood Pressure (mmHg)	69.81 ± 7.87	71.45 ± 5.56	$p < 0.42$	Not Significant

Table 3: Effect of sodium feredetate on gastrointestinal system

Indicators	Nausea	Vomiting	Diarrhoea	Constipation
Gastrointestinal system	NIL	NIL	NIL	Four (First few days)

change in blood pressure has been observed in the study group.

Table 3 shows that out of twenty two patients studied, four patients complained of constipation while on treatment, for the first few days. No other gastrointestinal side-effects were observed in all these patients throughout the study period.

Discussion

Of all the anaemias, iron deficiency anaemia (IDA) is the most common type of anaemia. Estimates from the World Health Organization report that 35% to 75% (56% on average) of pregnant women in developing countries are anaemic.[1] In India 49.7% of pregnant women are anaemic.[7]

The major factor responsible for development of iron deficiency in developing countries like India, is generally not just low iron intake, but rather low iron absorption also. Iron intake is often relatively high, unfortunately much of the iron ingested is poorly bioavailable. Iron absorption from habitual Indian diets is very low, varying between 2-3%.[8] Major cereals, legumes and staple foods contain high levels of phytic acid, which is a potent inhibitor of iron absorption and some such as sorghum, also contain phenolic compounds, which greatly impede iron absorption by binding iron in the gut into unabsorbable complexes.

Numerous iron compounds have been developed over the past decade for enhancing the bioavailability of iron, but generally the iron supplements available are associated with low bioavailability, undesirable metallic taste and gastrointestinal disturbances.

Sodium feredetate (NaFeEDTA or sodium iron ethylenediaminetetraacetic acid) has been suggested as an ideal iron compound for the treatment of IDA, especially in developing countries where cereals form the staple food and the EDTA moiety present in sodium feredetate, protects the iron from binding with phytic acid present in the cereals and thus increasing its bioavailability (International Nutritional Anaemia Consultative Group, 1993).[9]

Sodium feredetate is readily soluble in water. Once ingested, it passes through the stomach intact, where it remains complexed with EDTA under the acidic conditions prevailing in the stomach. The chelate holds the Fe in solution as the pH rises. Thus preventing Fe from binding with the phytic acid present in many cereals and legumes. Subsequently, it arrives in the upper small intestine but the strength of the complex is progressively reduced allowing release of Fe for absorption. Fe chelated by EDTA is available for absorption via the physiologically regulated pathways responsible for Fe uptake.[10] The mucosal cells that line the duodenum, split sodium feredetate into iron and EDTA.[10] The EDTA moiety stays behind in the gastrointestinal tract and is mainly excreted in the faeces.

The compound, sodium feredetate has been reported to be about 2-4 times better absorbed than $FeSO_4$ from a variety of meals containing cereals and legumes, as the absorption of Fe from sodium feredetate is less influenced by the presence of such inhibitory ligands.[11] Another important property of sodium feredetate is that sodium feredetate equilibrates with the common pool and the equilibration of sodium feredetate with the common pool iron, improves the bioavailability of intrinsic food iron as well.[12] Therefore, sodium feredetate improves iron balance by supplying iron in a form less affected by dietary inhibitors, but also improves the absorption of non-haem iron in the meal derived from other sources. It has also been recently approved as a food additive, by the Joint Expert Committee on Food Additives (JECFA, 1999).[13]

Will and Vilter[14] of the University of Cincinnati investigated the therapeutic efficacy of sodium feredetate in humans. They discovered that iron from sodium feredetate was utilised in haemoglobin formation. Candela *et al* administered 5mg of iron as $Na^{59}FeEDTA$ to six fasting human volunteers and the measured RBC utilisation was 12%.[10] Similar conclusions were reached in another human absorption study carried out by MacPhaiel *et al*.[12] Subsequently, more studies were conducted to determine the efficacy of sodium feredetate. Wegelius[15] worked on treating infants and young children in Aurora Hospital in Helsinki. She confirmed that the iron-deficient infants and young children responded well to sodium feredetate.

C.F. Herridge[16] at St. George's Hospital in London, conducted a comparative study using different iron supplements for the treatment of iron deficiency anaemia. He found that sodium feredetate gave the greatest rise in haemoglobin generation (0.57g/100ml/week) as compared to ferrous gluconate (0.40g/100ml/week) and ferrous succinate (0.35g/100ml/week).

Jarl Kahn[17] *et al* used this compound for the treatment of anaemia. Their study showed a significant increase in Hb levels immediately after the treatment period as well as 4 weeks later. Lin XM[18] *et al* in 2003, used sodium feredetate for the treatment of iron deficiency anaemia and showed significant rise in Hb levels. Also, from results of the current study, it appears that there is a significant ($p<0.05$) increase of haemoglobin levels of 1.8g/dL at the end of the study period.

The compound sodium feredetate is also used as a food additive to counter iron deficiency anaemia. Junsheng[19] *et al* (2002) studied the therapeutic effect of sodium feredetate – fortified soy sauce on anaemic students. They documented an increase in Hb, serum ferritin and decrease in total iron binding capacity in patients on

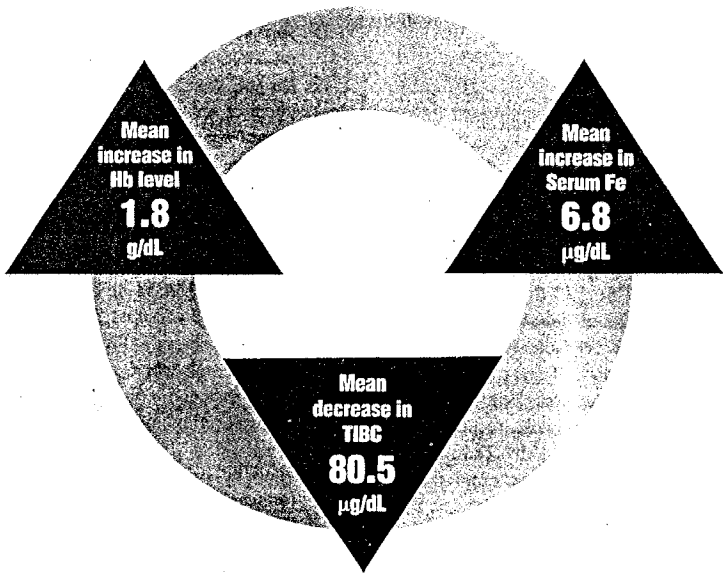

Fig. 3: Diagrammatic representation of mean increase in Hb and serum Fe and mean decrease in TIBC levels in the study group

sodium feredetate. Sodium feredetate has been used successfully in three fortification trials in the developing world to combat iron deficiency anaemia.[20-25] A large-scale study in Thailand where fish–sauce was enriched with sodium feredetate, led to a favourable increase in Hb levels in an adult population.[20,21]

Pham Van Thuy, Lena Davidsson *et al* (2003)[26] reported that regular consumption of iron-fortified fish sauce significantly reduced the prevalence of iron deficiency anaemia in Vietnamese women during a 6-month intervention trial. Fortifying fish sauce with iron by using a water soluble, highly bioavailable compound (NaFeEDTA) is a promising therapy for iron deficiency anaemia in Vietnam. Meredith C Fidler, Lena Davidsson[27] *et al* (2003) concluded that the relatively high iron absorption from NaFeEDTA fortified fish sauce and soy sauce indicates the potential usefulness of this iron fortificant.

As documented in Food and Chemical Toxicology, EDTA compounds are poorly absorbed in the gastrointestinal tract and do not undergo significant metabolic conversion, hence they have a low degree of oral toxicity.[25]

The compound is poorly absorbed, and that which reaches the bloodstream is eliminated by both glomerular filtration and tubular excretion. A small part (5%) of this split-off EDTA is able to enter the blood circulation, but is quantitatively excreted by the kidneys within 24 hours. Less than 1% of the sodium feredetate enters the blood circulation, but the kidneys quickly and completely remove it as well.[15,29]

The present study demonstrated no significant change in blood pressure or rise in serum sodium levels in the studied population.

The data collected and published over the past 20 to 30 years demonstrate that sodium feredetate is safe and effective for iron fortification of food products and meets the standard of **reasonable certainty of no harm.**[28] Based on the published record, sodium feredetate may be regarded as **Generally Recognized as Safe** (GRAS) [28] for the intended food uses and maximum use levels.

Sodium feredetate is not an iron salt, as it contains iron in an un-ionised form. In this compound the iron is "insulated" or "sequestered" with the sodium salt of ethylenediaminetetraacetic acid (EDTA) to form a chelate. As such it does not yield an astringent taste and does not stain the teeth.

Will and Vilter[14] in their study showed that with this compound gastrointestinal disturbances were infrequent. Hodgkins[30] revealed that iron preparations based on sodium feredetate did not yield astringent taste, did not stain teeth, and caused minimal gastrointestinal disturbances.

In the current study, four patients had constipation in the first few days, which was later, relieved on its own, without institution of any other therapy. No other undesirable side effects like nausea, vomiting and diarrhoea were documented in the present study.

Conclusion

Treatment with sodium feredetate in iron deficiency anaemia gives a satisfactory rise in haemoglobin levels with no serious side effects. Sodium feredetate is found to be efficacious in improving iron status in anaemic pregnant women and hence is a promising and future iron supplement, which overcomes the dilemma of effectiveness vs. taste and gastrointestinal side effects. The results of the study add to the body of evidence that sodium feredetate has a high bioavailability and minimal adverse effects and thus is a useful approach to combat iron deficiency in patients with iron deficiency anaemia.

Acknowledgement

We thank Ochoa Laboratories Ltd. for providing tablets of sodium ferredetate.

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