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ORIGINAL ARTICLE

Treatment of Iron Deficiency Anemia in Children: A Comparative Study of Ferrous Ascorbate and Colloidal Iron

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Abstract
Objective To compare the efficacy of ferrous ascorbate and colloidal iron in the treatment of iron deficiency anemia in children.
Methods Eighty one children, aged 6 mo to 12 y, were screened for iron deficiency anemia (IDA) and those diagnosed with IDA were randomized to receive ferrous ascorbate or colloidal iron for a period of 12 wk, such that each child received elemental iron 3 mg/kg body weight/d. Increase in hemoglobin (Hb) level was the primary outcome measure. Assessment was performed at baseline, wk 4, wk 8 and wk 12.
Results Of 81 children screened, 73 were included in the study. The mean rise in Hb at the end of the 12 wk was significantly higher in ferrous ascorbate group than the colloidal iron group [3.59±1.67 g/dl *vs*. 2.43± 1.73 g/dl; $P<0.01$]. Significantly higher proportion of children receiving ferrous ascorbate (64.86 % *vs*. 31.03 %; $P<0.01$) became non-anemic in comparison to colloidal iron.
Conclusions Ferrous ascorbate provides a significantly higher rise in hemoglobin levels in comparison to colloidal iron. The study supports the use of ferrous ascorbate in the pediatric age group, providing evidence for its role as an efficient oral iron supplement in the treatment of iron deficiency anemia.

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Introduction

Anemia is a major health problem in India, especially among women and children. The third National Family Health Survey (NFHS-3) [1] (2005–06) found that the prevalence of anemia among under-5 children approached 70 %. In children, anemia can result in weakness, diminished physical and mental capacity, increased morbidity from infectious diseases, impaired cognitive performance, motor development, and scholastic achievement [1]. Numerous studies have demonstrated that even moderate anemia (hemoglobin 7 to <10 g/dl) is associated with depressed mental and motor development in children, that may not be reversible [2].

Iron supplementation remains an important strategy for the prevention and treatment of iron deficiency anemia and can produce substantial improvements in the functional performance of iron deficient individuals [3]. The conventional ferrous salts are subject to oxidation by the alkaline environment and thereby results in reduced absorption and increased gastrointestinal (GI) side effects [4]. Ferrous ascorbate has been used as reference iron for many studies. Administration of iron in the form of ferrous ascorbate delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum gastrointestinal (GI) adverse effects [4].

Ascorbic acid has been shown to inhibit the effect of phytates, phosphates and oxalates on iron absorption. It also inhibits the conversion of ferrous to ferric iron; this leads to increased absorption of iron. Inhibition of conversion of ferrous to ferric iron reduces the amount of free radicals generated, thereby minimizing the GI adverse effects.

Ascorbic acid also facilitates iron absorption by the formation of soluble "iron ascorbate complexes" and by inhibiting the formation of chelates [5, 6]. Ferrous ascorbate has been shown to have bioavailability of 30.6 %–43.7 % in different studies [4]. An ascorbic acid -to-iron ratio (weight:weight) of approximately 6:1 (2:1 molar ratio) has been reported to increase iron absorption by 2 to 12 fold in several studies [7].

There are very few clinical studies on the efficacy of ferrous ascorbate as an oral iron supplement. These studies mainly concentrate on adults as the study population [4, 6, 8]. The present study was undertaken to evaluate the efficacy of ferrous ascorbate in the treatment of children with iron deficiency anemia and to compare its efficacy with colloidal iron.

Material and Methods

The current study (Study No: Zuv/Fern/Susp/2/2008) was carried out at a tertiary care outpatient pediatric hospital, 'Dr Yewale's Hospital & Vashi Criticare', Navi Mumbai, India. The study was conducted in accordance with the Declaration of Helsinki and ICH-GCP (International Conference on Harmonisation-Good Clinical Practice) Guidelines. All the children's parents gave their written informed consent before entering their child into the study. The protocol was approved by 'Jagruti-Independent Ethics Committee', Mumbai, India in October 2008.

The inclusion criteria were as follows: children between the age group of 6 mo to 12 y were eligible if they had anemia defined as hemoglobin (Hb) less than 10 g/dl. Anemia with iron deficiency was diagnosed on the basis of Guidelines by the British Society of Gastroenterology [9] which included the combination of at least two of the following criteria in addition to Hb<10 g/dl: lower than normal (80–100 fL) Mean Cell Volume (MCV), raised red cell volume distribution (RDW) than the normal range [11–15 %] or low serum ferritin levels (<12 ng/ml but not >100 ng/ml). The main exclusion criteria were: Anemia due to other causes than iron deficiency anemia, severe concurrent illness (cardiovascular, renal, and hepatic), known hypersensitivity to ferrous ascorbate or any other iron preparations, malignancy of any type, children with thalassemia major/aplastic or hypoplastic anemia, sickle cell anemia, hemolytic anemia or hemoglobinopathy and any other condition that in the opinion of the investigator did not justify the patient's inclusion.

The current study was an open–label, randomized, comparative study. Treatment was assigned as per the computer generated randomization sequence, using statistics software called WINPEPI Version 8.6. Each patient was supplied with the medication (ferrous ascorbate or colloidal iron) which would suffice for the study duration of 12 wk. Patients were assessed for the changes in the iron indices and adverse events at the time of enrollment and at the end of wk 4, wk 8 and wk 12. During each visit the investigator performed the clinical examination of the child, following which a trained research assistant collected blood through peripheral venous puncture with disposable syringe. Deworming of the child was done as a part of routine procedure before entering the child into the study. A routine complete blood count (CBC) which included the hemoglobin, hematocrit, red cell indices: the mean cell volume (MCV), mean cell hemoglobin (MCH) and mean concentration of hemoglobin per volume of red cells (MCHC), Red cell distribution width (RDW) and reticulocyte count was determined using Sysmex KX-21 cell counter at baseline (Day 0), wk 4, wk 8 and wk 12. Serum ferritin was measured using chemiluminescence immunoassay (CLIA) at baseline and at wk 12. HPLC studies on blood were done to exclude hemoglobinopathies at baseline. Follow-up was ensured by reminding the parent about the next follow-up visit of the child telephonically.

The dosage was calculated such that each child received elemental iron 3 mg/kg body weight/d. The dose administered to each child was calculated based on the child's body weight as measured on the day of the first blood sample.

The study medications used were: Ferrous ascorbate suspension, each 5 ml containing elemental iron 30 mg and folic acid 500 μg; Colloidal iron suspension, each 5 ml containing elemental iron 80 mg, folic acid 200 μg and vitamin B_{12} 2 μg. Parents were asked to return the study medication bottles at each visit which was used to evaluate the left over study medication in order to assess the dosage compliance. The amount of syrup used was approximated with the required amount that the child should have taken during the study period.

The primary study outcome was the increase in hemoglobin level at the end of each visit. The secondary outcome included the changes in other iron indices, responder rate defined as the proportion of children becoming non-anemic [Hb≥11 g/dl for children ≤5 y of age and Hb≥11.5 g/dl for children above 5 y of age] [10] at the end of the study and safety evaluation.

Statistical Analysis

All the statistically analyzed data are presented as mean ± standard deviation (SD), unless stated otherwise. The proportions of patients were reported as a percentage. Fisher's exact test was used to compare proportions, and student's t tests were used to compare means. *P* value less than 0.05 was considered significant. The sample size calculation was done based upon superiority parallel design. Considering a desired power of 90 %, allocation ration of 1:1, probability of Type I error of 5 %, common SD for baseline of 2 g/dl and the expected clinically relevant difference of 2 g/dl, it

was found that a minimum sample of 23 subjects in each arm was sufficient to provide statistically significant results.

Results

Demographic Data

Children were enrolled from November 2008 to December 2009. Of 81 patients were screened, 72 were randomised. Figure 1 shows the flow chart of patients throughout the study. Baseline demographic data are shown in Table 1. The age wise distribution of children are as follows- less than 2 y: 72.5 % [29/40] in ferrous ascorbate and 54.54 % [18/33] in colloidal iron, between 2 and 5 y of age: 20.0 % [8/40] in ferrous ascorbate and 33.33 % [11/33] in colloidal iron and above 5 y of age: 7.5 % [3/40] in ferrous ascorbate and 12.12 % [4/33] in colloidal iron.

Efficacy Evaluation

Hemoglobin

Hemoglobin levels before and after the interventions are displayed in Table 2. At the end of 12 wk, the mean rise in Hb was 3.59±1.67 g/dl (7.78±1.62 g/dl to 11.38±0.83 g/dl) in ferrous ascorbate group and 2.43±1.73 g/dl (7.49±1.88 g/dl to 9.92±1.83 g/dl) in colloidal iron group; $P<0.01$ between the groups. In the ferrous ascorbate group, 64.86 % of the children became non-anemic (Hb≥11 g/dl for children ≤5 y of age and Hb≥11.5 g/dl for children above 5 y of age) at the end of wk 12 while in the colloidal iron group it was only 31.03 % (Table 3). Applying Fisher's Exact test, the difference in responder rates of the two groups was found to be statistically significant with $P<0.01$.

Sub group analysis based on the severity of anemia is shown in Table 3. In children with severe anemia (Hb <7 g/dl) at baseline, the mean rise in Hb at the end of wk 12 was significantly higher in ferrous ascorbate group [5.43±1.12 g/dl *vs*. 3.14±2.29 g/dl; $P<0.01$]. In children with moderate anemia at baseline, the rise in Hb in ferrous ascorbate group was higher than colloidal iron group but did not reach statistical significance. However, it was observed that the proportion of children becoming non-anemic (Hb≥11 g/dl) in this group receiving ferrous ascorbate [76.0 %, 19/25] was significantly higher than those receiving colloidal iron [42.86 %, 9/21]; $P<0.05$ (Table 3).

Hematocrit

At baseline, 92.5 % [37/40] of the patients in ferrous ascorbate group had a hematocrit level <36 % while 7.5 % [3/40] had it within normal range [36–44 %], while in the colloidal iron group it was 87.10 % [27/31] and 12.99 % [4/31] respectively. At the end of wk 12, 43.24 % [16/37] of the

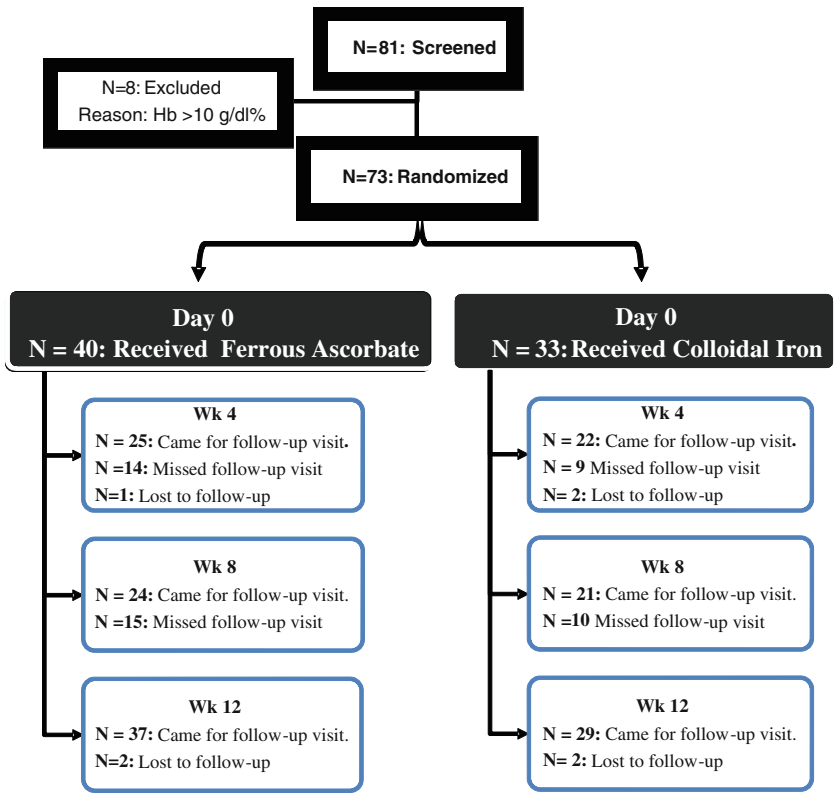

Fig. 1 CONSORT flow diagram showing number of patients enrolled in the study, randomized to each treatment group and reasons for discontinuation

patients in the ferrous ascorbate group and 41.28 % [12/29] in the colloidal iron group were within the normal range.

Mean Corpuscular Volume (MCV)

At baseline, all the patients [40/40] in the ferrous ascorbate group and 87.10 % [27/31] in the colloidal group had MCV less than 80 fL while the remaining 4 patients were normocytic [80–100 fL]. At wk 4, the improvement in the MCV was greater in the ferrous ascorbate group with a 21.95 % rise from the baseline as compared to 6.13 % in the colloidal iron group (Table 2).

Mean Corpuscular Hemoglobin (MCH)

At baseline, all the patients [40/40] in the ferrous ascorbate group and 96.77 % [30/31] in the colloidal iron group were hypochromic (MCH value <26 pg/cell). The improvement in ferrous ascorbate group was observed by wk 4, with a statistically significant 43.65 % rise in ferrous ascorbate group as compared to the 20.76 % rise in colloidal iron group from the mean baseline value (Table 2).

Mean Corpuscular Hemoglobin Concentration (MCHC)

In the ferrous ascorbate group 97.5 % [39/40] of the patients had their MCHC level <32.0 g/dL at the time of enrollment. One patient had MCHC level within the normal range [32.33–35.9 g/dL]. In colloidal iron group, 93.55 % [29/31] patients had their MCHC level <32.0 g/dL while 6.45 % [2/31] were within the normal range. At the end of the 12 wk, 75.68 % [28/37] and 50.0 % [14/28] of the patients in ferrous ascorbate and colloidal iron group respectively were within normal range.

Serum ferritin

At baseline, 95 % [38/40] of the children in the ferrous ascorbate group and 85.29 % [29/34] in the colloidal iron group had their serum ferritin level below the normal values. After 12 wk of therapy, a significant rise was observed in both the treatment groups, from 7.71±6.79 ng/ml to 98.3±119.2 ng/ml in the ferrous ascorbate group and from 19.6±19.35 ng/ml to 60.51±78.39 ng/ml in the colloidal iron group. At the end of the study, 96.96 % [32/33] of children in the ferrous ascorbate group were within the normal values while in the colloidal iron group it was 53.85 % [14/25].

Safety Evaluation

Overall both the formulations were well tolerated. No serious adverse events were reported by any parent during the treatment of their children with either iron formulation.

Discussion

Ferrous ascorbate has been used as a reference iron formulation in many iron bioavailability and food fortification studies [11–14]. In patients subjected to orthopaedic surgery and autotransfusion, receiving iron treatment for 2 mo after surgery attained better results with ferrous ascorbate and it was better tolerated than ferrous sulphate [8]. In a comparative study between ferrous ascorbate and carbonyl iron in male and non-pregnant female patients (age:18–60 y) diagnosed with IDA, ferrous ascorbate resulted in a significantly higher rise in Hb in comparison to carbonyl iron (5.03±1.81 g/dL *vs*. 2.82±1.43 g/dL) after 60 d of treatment [4]. In HERS trial, 1461 women (pregnant and non-pregnant women), administered ferrous ascorbate-folic acid combination

Table 1 Baseline characteristics of the study population

		Ferrous ascorbate	Colloidal iron	*P* value between the groups
N		40	33	
Gender	Male	(25/40) 62.5 %	(17/33) 51.51 %	NS
	Female	(15/40) 37.5 %	(16/33) 48.48 %	NS
Age (y)	Mean ± SD[a]	2.05±2.33	2.72±2.83	NS
	Range	0.5–12	0.5–12	
Body weight (kg)	Mean ± SD[a]	9.14±2.79	11.21±5.44	NS
	Range	6.19–22	6.0–30.5	
Severity of anemia	Severe (Hb: <7 g/dl)†	35.5 % (13/40)	27.27 % (9/33)	NS
	Moderate (Hb: 7-<10 g/dl)†	67.5 % (27/40)	72.72 % (24/33)	NS
HbA_2 (%)	HbA_2 levels of all the children were in normal range, excluding the presence of beta-thalasemia trait			

[a]Students' t-Test; †Fisher's exact test; *NS* Non Significant (*P*>0.05)

Table 2 Hematological parameters for all the children

Parameters	Drug	*N*	Day 0	Wk 4	*N*	Day 0	Wk 8	*N*	Day 0	Wk 12
Hb (g/dl)	Fe Asc	25	7.53±1.68	10.20±1.01*†	24	7.74±1.46	10.65±1.16*†	37	7.78±1.62	11.38±0.83*†
	C. Iron	22	7.68±2.18	9.35±2.01*	21	8.21±1.18	9.73±1.59*	29	7.49±1.88	9.92±1.83*
Hct (%)	Fe Asc	25	29.50±5.23	34.07±4.12*	25	30.41±4.20	34.93±4.71*	37	30.09±4.67	35.71±3.42*
	C. Iron	20	29.19±6.87	31.58±6.71*	20	31.57±4.36	34.42±4.62*	27	29.06±5.98	33.32±4.64*
MCV (fL)	Fe Asc	23	62.17±6.42	75.82±10.12*	22	62.20±5.53	74.93±10.35*†	35	62.54±6.73	79.53±9.52*†
	C. Iron	19	70.05±11.94	74.35±11.50	19	69.59±12.24	74.81±7.86	26	66.01±9.65	75.66±11.48*
MCH (pg/cell)	Fe Asc	25	16.01±3.04	22.99±4.35*	24	15.61±2.71	23.14±3.92*†	37	16.25±3.17	24.83±5.57*
	C. Iron	19	17.96±5.17	21.69±4.95*	19	18.24±4.40	21.33±3.97*	26	16.70±4.24	22.44±5.54*
MCHC (g/dL)	Fe Asc	25	25.69±3.38	30.13±2.60*	24	25.07±2.30	30.75±2.34*†	37	25.90±3.11	31.97±1.97*
	C. Iron	19	25.28±4.05	29.01±4.19*	19	26.01±2.42	28.39±3.71*	26	25.06±3.45	29.35±4.10*

All values are represented as Mean ± SD. * *P vs*. Baseline <0.05; † *P* value between the two treatments <0.05; *Fe Asc* Ferrous Ascorbate; *C. Iron* Colloidal Iron; *Hct* Hematocrit; *MCV* Mean Cell Volume; *MCH* Mean Cell Hemoglobin; *MCHC* Mean Concentration of Hemoglobin Per Volume of Red Cells

for 45 d showed a significant rise in Hb from 8.53± 1.46 g/dL to 10.90±1.41 g/dL [6].

The present phase IV (post-marketing) study was conducted to evaluate and compare the efficacy and safety of two oral iron supplements, in the treatment of iron deficiency anemia in pediatric population. Both the iron salts used as study medications are marketed in India as tablet, syrup or drops to facilitate its utility in all the age groups. The study follows an open-label randomized design. Thus investigator bias towards administration of the study medication was avoided. Further, the results of the study were based on laboratory investigation assessment (CBC, ferritin levels in blood). The lab technicians were not aware the medication being consumed by the patient.

The recommended dosage for iron supplementation based on various guidelines ranges from 1 to 6 mg of elemental iron/kg/d based on the age and birth weight of the child [15–17]. The dose of 3 mg/kg/d of elemental iron used in this study was based on The CDC (Centers for Disease Control and Prevention) and the Institute of Medicine which recommends parental dietary counseling, treatment with oral ferrous salt at 3 mg/kg/d for 3 mo to restore iron stores, and monitoring of hemoglobin or hematocrit to assess response [18].

The high drop-out in follow-up visits could be attributed to age group of the study population, withdrawal of blood at each visit; long duration of the study [3 mo] and the fact that mild or moderate iron deficiency anemia may not show any alarming symptoms that would require immediate treatment, leading the parent not to take the condition seriously. The current study has its limitation in terms of smaller sample size and a wide range of age group been investigated. Future studies should evaluate this parameter in a selected age group of children. There were no side-effects reported by parents in either treatment group. In controlled clinical trials the incidence of adverse events was reportedly 11 % or less [6, 8].

Table 3 Effect on Hb levels after 12 wk of treatment

Group	Drug	*N*	Day 0	Wk 12	
			Hb, g/dl [Mean ± SD]	Hb, g/dl [Mean ± SD]	Responder rate[#] N (%)
All the children	Fe Asc	37	7.78±1.62	11.38±0.83*†	24 (64.86) ‡
	C. Iron	29	7.49±1.88	9.92±1.83*	9 (31.03)
Severe anemia at baseline	Fe Asc	12	5.75±0.99	11.18±0.65*†	6 (50.0) ‡
	C. Iron	8	5.18±1.86	8.31±2.25*	0 (0.0)
Moderate anemia at baseline	Fe Asc	25	8.76±0.65	11.47±0.90*	18 (72.0)
	C. Iron	21	8.37±0.87	10.53±1.22*	9 (42.9)

Fe Asc Ferrous Ascorbate; *C. Iron* Colloidal Iron; **P*<0.05 *vs*. baseline (*t* test); † *P*<0.05 between groups (*t* test); ‡ *P*<0.05 between groups (Fisher's test)

#Responder rate defined as the proportion of children with Hb≥11 g/dl for children ≤5 y of age and Hb≥11.5 g/dl for children above 5 y of age, after 12 wk of therapy

Conclusions

Ferrous ascorbate was more effective than colloidal iron in treating iron deficiency anemia in children when both were administered at a dose of 3 mg/kg elemental iron each day.

The current study provides evidence that ferrous ascorbate is an effective and well tolerated therapeutic agent in the pediatric age group.

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Contributions VNY was involved in the review of the study protocol, conducting the study in accordance with the standards of GCP, data analysis and revision of the manuscript drafts. BD was involved in the conceptualization of the study, designing of the protocol, initiation, supervision, auditing and monitoring of the site, interpretation of the data and statistical outcomes and revision of the manuscript drafts.

Conflict of Interest VNY has no financial relationships with Zuventus Healthcare Ltd that might have an interest in the submitted work in the previous 3 y and no other relationships or activities that could appear to have influenced the submitted work.BD is employee of Zuventus Healthcare Ltd.

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