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RESEARCH ARTICLE

Comparative evaluation of efficacy of ferrous ascorbate and ferrous calcium citrate prepared in multidrug delivery system on haemoglobin status in anaemic pregnant women

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Abstract

Iron deficiency anaemia (IDA), the most prevalent nutritional deficiency leading to mortality globally. Oral ferrous salts are effectively used to treat iron deficiency in pregnancy. For the present study, no direct comparison demonstrating the efficacy of ferrous ascorbate and ferrous calcium citrate was considered. An open-label, observational study was designed and conducted for two months. Subjects were randomly allocated to two groups (Group A and Group B). The medication followed in Group A was, ferrous calcium citrate with elemental iron 50 mg; In Group B ferrous ascorbate containing elemental iron 100 mg orally for two months at bedtime. Haemoglobin levels, other hematological parameters, weight changes, side effects, conjunctival colour and general wellbeing were assessed in every visit (i.e. 0, 30th and 60th day) for clinical efficacy assessment. There was increase in the mean serum haemoglobin and ferritin levels ($p<0.05$). In Group A and Group B the mean values of all the assessment parameters increased significantly ($p<0.05$) in follow-up visits (i.e. 1st month and 2nd month) when compared to baseline values. Out of 69 adverse drug events, 29 (42%) were reported from Group A and 40 (58%) from Group B. Ferrous calcium citrate showed considerable efficacy and safety profiles.

Keywords: Iron deficiency; anaemia; haemoglobin; ferrous calcium citrate; ferrous ascorbate

Introduction

Anaemia is a common medical disorder that contributes significantly to maternal morbidity and mortality, intrauterine growth retardation, preterm delivery and perinatal morbidity and mortality.[1–3] The prevalence of anaemia ranges from 33% to 89% among pregnant women with wide variations in different regions of the country.[4] In India $\geq$ 90% of anaemia cases are estimated to be due to iron deficiency because high iron requirements during pregnancy are not easily fulfilled by dietary intake, especially when bioavailability of iron is poor.[5–7]

Nutritional iron deficiency is highest in population segments that are at a peak rate of growth, namely, infants, young children and pregnant women. Pregnancy is a time in which the risk for developing iron deficiency anaemia is highest because iron requirements are substantially greater than average absorbable iron intakes. Physiologic demands for iron increases from 0.8 to $\leq$ 7.5 mg.[8,9]

Diet alone cannot supply the 30-40 mg of iron that is required for the absorption of the 4-6 mg needed during the latter stages of pregnancy. Iron supplementation is strongly recommended for all pregnant women in developing countries. Oral iron intake is the treatment of choice and almost all the women can be treated effectively with oral iron preparations.[10–12]

Currently, there are many iron preparations available containing different types of iron salts, including ferrous sulfate, ferrous fumarate, ferrous ascorbate and ferrous bisglycinate. Ferrous calcium citrate is prepared in multi-drug delivery system, which ensures iron delivery in the duodenum with the minimal gastric irritation. Micronized ferrous calcium citrate with an acid-resistant coat is well tolerated. Ferrous ascorbate is one of the most common iron preparations used in pregnancy. With these viewpoints, the present comparative efficacy evaluation of ferrous ascorbate and ferrous calcium citrate study was undertaken considering the fact that there is no direct comparison demonstrating the efficacy of ferrous ascorbate and ferrous calcium citrate.

Methods

Study design

An open-label, observational study was designed to conduct for a period of two months in pregnant women visiting OBG Department of S. S. Institute of Medical Sciences and Research Centre, Davangere. Patients were asked to sign in informed consent forms after study details are explained to them. Patients were randomly allocated to two groups of 25 each i.e. Ferrous calcium citrate (Group A) and ferrous ascorbate (Group B). Institute Ethics Committee's approval certification for Human Research was sought and obtained before the study was started.

Study subjects

Pregnant women visiting the outpatient department were included in the study independent of gestational age, obstetric score and age specification whose baseline haemoglobin and other hematological parameters were evaluated.

At first visit after recording the patient details, study medications were provided for two months duration. Patients were instructed to report for the follow up after every month for successive two months. The date of visits was informed to them at the time of drug distribution. At each visit, after taking aseptic precautions, patient venous blood samples were drawn in EDTA vacutainer tubes for the assessment of haemoglobin levels and red cell indices. Analysis was done on the same day of blood collection. Changes in weight and adverse events were recorded in the patient case report form.

Study medications

- Ferrous calcium citrate with elemental iron 50 mg at bedtime + calcium carbonate 500 mg, vitamin D3 200 IU, Magnesium hydroxide 90 mg, Zinc Sulphate Monohydrate USP 4 mg at bedtime for the period of two months.
- Ferrous ascorbate containing elemental iron 100 mg orally for two months at bedtime.

Inclusion criteria

- Pregnant women not taking any iron preparations
- Pregnant women with gestational age less than 6 month.
- Anaemia with haemoglobin between 7gm% and 10.5 gm%.
- Pregnant women between the age Group Between 18 years and 40 years.

Exclusion criteria

- High-risk pregnancy with cardiac and other complications.
- Gastric blood loss, renal disorders, hemoglobinopathies, vitamin B12 and folic acid deficiency, constipation.
- Women intolerant to iron derivatives, women with antepartum haemorrhage and those who delivered within two months of starting iron therapy.
- Persons who were irregular in their routine check-ups and did not take iron supplements daily as prescribed.
- Persons with medications that can interfere with iron absorption.
- Persons having a history of parasitic infections such as hookworm anaemia.
- Diet not balanced and without proper nutrition.

Treatment plan

After random allocation patients were prescribed ferrous calcium citrate or ferrous ascorbate for two months with regular follow-up at the end of each month.

Study procedure

At first visit after recording the patient details, study medications were provided for two months duration. Patients were instructed to report for the follow up after every month for successive two months. The date of visits was informed to them at the time of drug distribution. At each visit, after taking aseptic precautions, patient venous blood samples were drawn in EDTA vacutainer tubes for the assessment of haemoglobin levels and red cell indices. Analysis was done on the same day of blood collection. Changes in weight and adverse events were recorded in the patient case report form.

Patients were instructed to take medications under study regularly with a regular diet and activity. Haemoglobin levels and other hematological parameters were assessed in every visit (i.e. 0, 30th and 60th day). Weight changes, side effects were monitored regularly.

Efficacy and compliance

Patients were asked for generalized wellbeing and conjunctival colour, weight change was also being taken into consideration for clinical efficacy assessment. Laboratory assessment for efficacy was done based on improvement in haemoglobin levels and other hematological parameters.

Adverse effects

Nausea, vomiting, gastric irritation, giddiness, lethargy, headache, pain abdomen, constipation, etc. if any were noted.

Results

The mean serum haemoglobin (Hb) levels at baseline in group A and group B were 8.56±1.12 mg/dL and 9.028±0.98 mg/dL respectively. Whereas the serum Hb levels at follow-up visits (i.e. 1st month and 2nd month) were increased as compared to baseline serum Hb values. However, the mean differences between baseline, 1st month and 2nd month were not statistically significant (p>0.05) (Table 1).

Table 1. Mean serum haemoglobin levels at different follow-up visits.

Visits	Group A	Group B	t-value	p-value
Baseline	8.56±1.12	9.028±0.98	-1.57	0.122
1 Month	9.28±1.06	9.756±0.73	-1.847	0.072
2 Months	10.20±0.87	10.44±0.67	-1.079	0.286

Similarly, the mean serum ferritin levels at baseline in group A and group B were 10.48±1.05 mg/dL and 8.48±1.05 mg/dL respectively. Whereas the serum ferritin levels at follow-up visits (i.e. 1st month and 2nd month) were increased as compared to baseline serum ferritin values. Furthermore, the mean differences between baseline, 1st month and 2nd month were statistically significant (p<0.05) (Table 2).

Table 2. Mean serum ferritin levels at different follow-up visits.

Visits	Group A	Group B	t-value	p-value
Baseline	10.48±1.05	8.48±1.05	6.76	0.000
1 Month	21.52±1.05	19.32±1.32	6.55	0.000
2 Months	32.12±1.05	29.08±1.35	8.87	0.000

In Group A the mean values of all the assessment parameters of study participants were increased significantly (p<0.05) when compared baseline values with 2nd month visit values (Table 3).

Table 3. Mean change in assessment parameters in Group A

Variables	Baseline	After 2 months	t-value	p-value
Hb	8.56±1.056	10.28±0.784	-8.793	<0.05
Weight	48.64±8.62	52.32±8.20	-16.076	<0.05
MCV	70.52±1.710	75.96±1.540	-13.732	<0.05
MCH	21.04±0.734	23.28±0.737	-12.736	<0.05
MCHC	29.92±1.037	31.16±1.027	-8.57	<0.05
Serum Ferritin	10.48±1.05	32.12±1.05	-76.7	<0.05

Similarly, in Group B the mean values of all the assessment parameters of study participants was increased significantly (p<0.05) when compared baseline values with 2nd-month visit values (Table 4).

Table 4. Mean change in assessment parameters in Group B

Variable	Baseline	After 2 months	t-value	p-value
Hb	9.028±0.98	10.44±0.67	-7.743	<0.05
Weight	47.00±7.638	50.84±7.609	-8.834	<0.05
MCV	71.12±1.24	75.12±1.64	-13.333	<0.05
MCH	20.52±0.823	22.36±1.114	-7.184	<0.05
MCHC	31.04±0.935	31.72±0.980	-3.778	<0.05
Serum Ferritin	8.48±1.05	29.08±1.35	-81.84	<0.05

A total of 69 adverse drug events were observed in 50 patients during the study period. The most common adverse

event was nausea and vomiting (29) followed by lethargy (26). Out of 69 adverse drug events, 29 (42%) were reported from Group A and 40 (58%) from Group B (Figures 1 and 2).

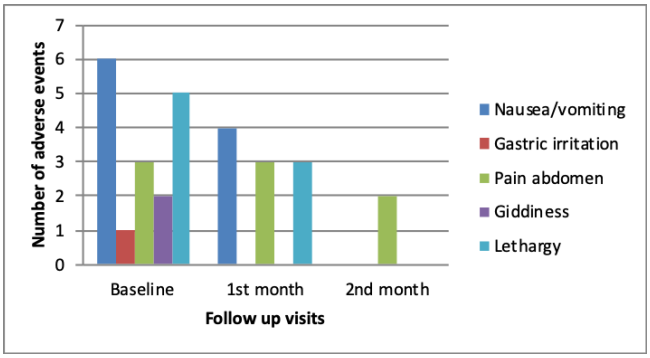

Fig 1. Adverse events observed in Group A

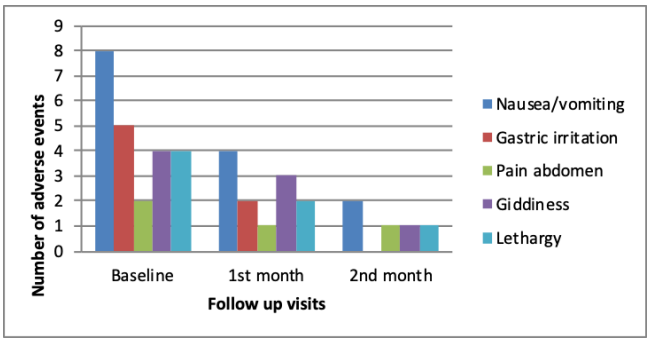

Fig 2. Adverse events observed in Group B

Discussion

Iron deficiency anaemia (IDA) is one of the most prevalent nutritional deficiencies in the world and 12th most important risk factor for all mortality globally.[13] The iron deficiency can be effectively prevented and treated by using a nutritional diet, different oral and parenteral iron preparations as well as with blood transfusion.[14] Oral ferrous salts are most commonly used effectively to treat iron deficiency in pregnancy.

Our study findings showed the outcomes of total 50 patients treated with ferrous calcium citrate (Group A) and ferrous ascorbate (Group B) with 25 study subjects each for two months conducted in a tertiary care teaching hospital of South India. During 2 months of follow up, all the 50 patients remained on treatment with no deaths or dropouts. Before the study start up, we observed fatigue and breathlessness as most common presenting symptoms among the study participants. This was mainly because of the low oxygen-carrying capacity and decreased oxygenation of skeletal muscle in anaemia patients.[14] Along with symptoms, pallor of tongue, nail and conjunctiva was also observed, and its severity was related to haemoglobin concentration. Similar findings had been reported in studies conducted by Tokars et al. 2010.[15]

Different hematological parameters like haemoglobin, anaemic indices like MCV, MCH and MCHC, serum ferritin levels were investigated to diagnose the anaemia in baseline and as well as in month 1 and month 2 to evaluate the improvements in hematological parameters. The results of our study revealed that the baseline value of laboratory parameters as well as clinical symptoms was comparable with the other two follow up visits. Treatment of ferrous calcium citrate and ferrous ascorbate resulted in significant improvement in fatigue and breathlessness at first follow up itself. Further, all patients were symptom-free at the end of 2nd month. Similar results were documented in studies carried out by Suheyl Asma et al. 2009 and Gabriel Mircescu et al. 2006.[16,17] As a result of treatment with oral iron preparations improved availability of elemental iron for erythropoiesis and that improved signs and symptoms of anaemia.[18]

A parallel improvement in laboratory parameters was observed in our study. The mean increase in haemoglobin levels, anaemia indices like MCV, MCH, MCHC and serum ferritin levels showed increased values among both the groups. Even though there was no significant difference between the two groups, ferrous calcium citrate showed considerable improvements in the laboratory levels due to its high absorption rates when compared with ferrous ascorbate. Ferrous calcium citrate, after administration, gets dissociated into calcium citrate and iron. Calcium citrate in the stomach binds to the phytates and phosphates present in the food and decreases their inhibitory effect on iron absorption.[19]

The study also showed that these two iron preparations were well tolerated and there no serious adverse events were observed. The adverse events like nausea, vomiting, gastric irritation, giddiness, lethargy, headache, abdominal pain were reported more in group B when compared to group A. All these findings clearly state that the efficacy of ferrous calcium citrate is high when compared with ferrous ascorbate.

Conclusion

Iron-deficiency anaemia is a global health problem, where pregnant women represent one of the most vulnerable groups, because of the enhanced iron requirement to meet mothers' and the fetus' supplement needs. Our study findings depicted that ferrous calcium citrate showed considerable efficacy and safety profiles than ferrous ascorbate. Therefore, ferrous calcium citrate would be the preferred choice for the treatment of iron deficiency anaemia in pregnant women.

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