Comparison between oral ferrous ascorbate and colloidal iron in the treatment of iron deficiency anemia

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ABSTRACT

Background: Anemia is a global health issue. There is association of impaired cognition and iron deficiency anemia. Ferrous and ferric forms of oral iron preparations are available for the treatment of iron deficiency anemia. This study was conducted with an aim to compare the efficacy and safety of oral ferrous ascorbate and colloidal iron in the treatment of iron deficiency anemia.

Methods: It was a prospective interventional study with 12 weeks of treatment protocols alternatively assigned to children diagnosed with iron deficiency anemia. Patients received either of two iron preparation used in study and they were assessed at week 0, 4, 8 and 12.

Results: Hemoglobin (gm%) significantly increased from 7.40 to 12.87 in ferrous ascorbate group and from 7.24 to 11.32 in colloidal iron group at the end of 12 weeks of treatment (p<0.05). There was significant increase in corrected reticulocyte count (%) from 0.52 to 1.39 in ferrous ascorbate group and from 0.42 to 1.27 in colloidal iron group (p<0.05). Serum ferritin (mcg/liter) was also significantly increased from 11.54 to 21.53 in ferrous ascorbate group and from 10.57 to 20.52 in colloidal iron group at the end of 12 weeks (p<0.05).

Conclusions: The present study concluded that the ferrous ascorbate is an efficient oral iron supplement in the treatment of iron deficiency anemia in the pediatric age group compared to colloidal iron.

Keywords: Anemia, Ferrous ascorbate, Colloidal iron

INTRODUCTION

Anemia is decrease in the oxygen carrying capacity of blood due to reduction in hemoglobin concentration or volume of RBC below the normal range for respective age group. Anemia is defined as a hemoglobin level that is two standard deviations below the mean for age and sex. Globally, anemia affects approximately 24.8% of the population. The prevalence of anemia is highest in preschool-age children and it is 47.4%.¹ In India, in 2015-16, 56% of 6- to 59-month-old children were diagnosed to have anemia—a decrease of only 13.5 percentage points since the NFHS-3 study conducted in 2005-06.² Microcytic iron deficiency anemia is the most common cause of childhood anemia.

There is an association of impaired neurocognitive function in infancy with iron deficiency anemia. Irreversible long term cognitive defects are also possibly associated with it.¹ Hemoglobin is protoporphyrin, each molecule having 4 iron containing heme residues. Therefore, iron supplementation is the management of iron deficiency anemia.

Oral iron preparations are available in the form of ferrous and ferric salts. Ferric forms are poorly soluble in acidic medium. Ferric forms are reduced to ferrous before absorption by duodenal cytochrome B reductase. All dietary iron has to be converted to ferrous form to make it accessible to intestinal mucosal cells. Various ferrous salts available are ferrous sulphate (hydrated salt 20%,
dried salt 32% iron), ferrous ascorbate (14% iron), ferrous gluconate (12% iron), ferrous fumarate (33% iron). Absorption from chelated iron is four times higher than ferrous sulfate.4

Colloidal iron has more iron content than ferrous salt and better tolerability with lesser side effects but rise of hemoglobin with it is still not assured. It is very much important to treat anemia with effective drug to prevent series of events occurring due to it.

As there is paucity of studies directly comparing ferrous ascorbate and colloidal iron in pediatric age group, this study was undertaken with the aim to compare oral ferrous ascorbate and colloidal iron in the treatment of iron deficiency anemia in terms of safety and efficacy.

METHODS

It was a prospective interventional study with 12 weeks treatment protocol conducted at department of pediatrics, Geetanjali medical college and hospital, Udaipur from January 2019 to December 2019. The study was conducted after the approval of institutional ethical committee. Details of the study were explained to the parents of each child and written informed consent was obtained voluntarily. Children between age group of 6 months to 12 years were diagnosed with iron deficiency anemia having both features Hb<2SD for age and gender and low serum ferritin level<12 μg/l were included in the study.

Children were assigned in two groups alternatively to receive either of two iron preparation used in study i.e., ferrous ascorbate and colloidal iron. The dosage of iron preparation was decided based on the body weight and each child received 6 mg/kg/day of elemental iron once a day. Deworming was done as a routine procedure before the child enters the study.

Patients were assessed for the changes in the iron indices (haemoglobin, hematocrit, red cell indices: mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration, red cell distribution width and reticulocyte count) at the time of enrolment (day 0), week 4, week 8 and the end of week 12. Serum ferritin was done at the time of enrollment and at the end of 12 week. Patients were followed up at week 4, 8 and 12 for any side effects and compliance. Data was collected in a case record form at day 0, week 4, week 8 and week 12.

During each visit complete general physical examination was done. History was taken for any adverse effects and compliance.

Statistical analysis

Collected data was entered in Microsoft excel. Descriptive data was presented as mean ± standard deviation. Proportion of patients was reported as percentage. Statistical analysis was done using software statistical package for social sciences (SPSS) version 25. Students t test (paired/unpaired) was used for quantitative data. Chi-square test and Mc Nemar test was be used for categorical data. P value<0.05 was considered statistically significant.

RESULTS

Total 50 children of either gender, aged 6 months to 12 years were enrolled. All were divided into two groups (25 in each) to receive either of drug to be used in the study. The maximum number of children in the age group of 2 to 6 years were diagnosed to have iron deficiency anemia. There was no significant difference in the prevalence of iron deficiency anemia in male and female children. Maximum number of children were found to have to moderate iron deficiency anemia (Table 1).

Table 1: Demographic profile of all the children in both the groups.

| Demographic profile | Ferrous ascorbate (n=25) (%) | Colloidal iron (n=25) (%) |
|---------------------|-----------------------------|--------------------------|
| Age (years)         |                             |                          |
| <2                  | 3 (12)                      | 0                        |
| 2-6                 | 12 (48)                     | 15 (60)                  |
| 7-10                | 6 (24)                      | 5 (20)                   |
| 11-12               | 4 (16)                      | 5 (20)                   |
| Gender              |                             |                          |
| Male                | 13 (52)                     | 14 (56)                  |
| Female              | 12 (48)                     | 11 (44)                  |
| Grading of anemia (gm%) |                     |                          |
| Severe (<7)         | 7 (28)                      | 6 (24)                   |
| Moderate (7.0-9.9)  | 18 (72)                     | 19 (76)                  |

Table 2: Comparison of haematological parameters and iron indices in both groups before and after treatment.

| Parameters          | Ferrous ascorbate | Colloidal iron |
|---------------------|-------------------|----------------|
|                     | Day 0             | Week 12        | Day 0             | Week 12          | P value |
| Hb (gm%)            | Mean ± SD         | Mean ± SD      | Mean ± SD         | Mean ± SD        |        |
|                     | 7.40±1.07         | 12.86±0.21     | 7.23±1.39         | 11.32±0.95       | 0.12*   |
| Hct (%)             | 22.95±3.17        | 39.89±0.95     | 22.44±3.32        | 35.10±2.75       | 0.000*  |
| MCV (fl)            | 62.92±1.87        | 81.10±1.25     | 64.31±1.48        | 80.79±0.98       | 0.047*  |

Continued.
In the current study, it was found that the of all patient diagnosed to have iron deficiency anemia maximum children had moderate anemia. Similar results were found in some other studies. The difference in the severity of anaemia could be due to study area, cultural variation, lifestyle, socio economic, dietary habit and sample size.

In the current study the significant difference in the mean haemoglobin level in male and female children in both the groups. However, Gerardo et al study concluded that high proportion of gender difference was seen only after menarche suggesting iron deficiency anemia. A cross sectional study was done by John et al where they found that male and female children have equal susceptibility to iron deficiency anemia. Behera et al has carried out a cross sectional community based survey in children under 12 years of age and found that there is no significant difference in mean Hb level between male and female of both the groups. Sahu et al study also reached the same conclusion that the difference in mean haemoglobin level in male and female children was not significant. No literature is available on showing higher prevalence in particular gender in infants and children.

In the current study, it was found that the post treatment rise in Hb (gm%) levels were found to be higher in the ferrous ascorbate group as compared to the colloidal iron group. Similar results were also found in some other studies. The significant rise of mean haemoglobin level in male and female children was not significant. The rise in red cell indices are indicative of enhanced erythropoiesis after iron supplementation.

Hemoglobin (gm%), hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC count, reticulocyte count and serum ferritin increased significantly at the end of 12 weeks (p<0.05). Adverse effects were more in the ferrous ascorbate group compared to colloidal iron group. Diarrhea, nausea, vomiting, constipation and gastritis were common side effects (Table 2 and 3).

### DISCUSSION

Anemia is a global health related issue highly prevalent in pre-school children. Anemia can affect children in different ways. Anemic children have poor growth and development. Iron deficiency leads to impaired cognitive and psychomotor function and poor achievement in school. Deficit associated with iron deficiency are shown to be irreversible.

Maximum number of children in the age group of 2-6 years were diagnosed with iron deficiency anemia in both the groups. Kanchana et al study, reported that 77.8% of under five children were diagnosed to have anemia and also found that diarrhea was the chief symptom associated with anemia in more than half of the cases studied. Saba et al study has also reported anemia in 72.79% of children below 5 years of age. The common cause of anemia in the age group of 2-6 years may be due to delayed weaning, inadequate intake, frequent infection, increased demand or milk protein intolerance due to cow’s milk.

In the present study no significant difference was found in the prevalence of iron deficiency anemia in male and female children in both the groups. However, Gerardo et al study concluded that high proportion of gender difference was seen only after menarche suggesting iron deficiency anemia. A cross sectional study was done by John et al where they found that male and female children have equal susceptibility to iron deficiency anemia. Behera et al has carried out a cross sectional community based survey in children under 12 years of age and found that there is no significant difference in mean Hb level between male and female of both the groups. Sahu et al study also reached the same conclusion that the difference in mean haemoglobin level in male and female children was not significant. No literature is available on showing higher prevalence in particular gender in infants and children.

In the current study, it was found that the of all patient diagnosed to have iron deficiency anemia maximum children had moderate anemia. Similar results were found in some other studies. The difference in the severity of anaemia could be due to study area, cultural variation, lifestyle, socio economic, dietary habit and sample size.

In the current study the significant difference in the mean hemoglobin was seen after treatment with ferrous ascorbate and colloidal iron at the end of week 12. The study showed that the post treatment rise in Hb (gm%) levels were found to be higher in the ferrous ascorbate group as compared to the colloidal iron group. Similar results were also found in some other studies. Patil et al study have compared ferrous ascorbate (FA) and iron polymaltose complex (IPC) for treating IDA in children and found that rise in hemoglobin was more with ferrous ascorbate than with IPC. The significant rise of mean haemoglobin in ferrous ascorbate group could be due to better absorption of ferrous iron. Ferrie forms are poorly soluble in acidic medium and need to be reduced to ferrous form before absorption by duodenal cytochrome B reductase to make it accessible to intestinal mucosal cell.

In the current study it was observed that there was a significant increase in the levels of Hct (%), mean MCV (fl), mean MCH (pg/cell) and mean MCHC (g/dl) in the ferrous ascorbate group as compared to the colloidal iron at the end of week 12. Similar results were found by Ganguly et al. The rise in red cell indices are indicative of enhanced erythropoiesis after iron supplementation.

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**Table 3: Comparison of side effects in both the groups after treatment.**

| Side effects | Ferrous ascorbate (N) | Colloidal iron (N) | P value |
|--------------|-----------------------|--------------------|---------|
| Diarrhea     | 4                     | 2                  | 0.031*  |
| Nausea and vomiting | 4                     | 2                  | 0.028*  |
| Constipation | 4                     | 1                  | 0.021*  |
| Metallic taste | 5                     | 4                  | 0.451   |
| Staining teeth | 6                     | 5                  | 0.604   |
| Gastritis    | 4                     | 1                  | 0.012*  |

*P<0.05
Panchal et al study also compared the efficacy of ferrous ascorbate and sulphate in anemic patient of chronic kidney disease (CKD) and at end of 12 weeks it was found that mean rise in hemoglobin and other indices was significantly more with ferrous ascorbate as compared to ferrous sulphate.  

There was a statistically significant difference among the two groups with respect to mean RC (%) in week 4, 8, and 12 showing a significant increase in the RC (%) levels in the ferrous ascorbate group compared to colloidal iron group. Susanne et al conducted a study in patients of chronic rheumatologic disease to evaluate the hematological parameters predicting the response of oral iron therapy in chronic inflammation and concluded that, the response after six weeks of iron supplementation is best predicted by increase in reticulocyte count, reticulocyte hemoglobin, transferrin saturation and serum iron level. They also reported that the reticulocyte hemoglobin content increases after one week of oral iron therapy. In response to iron therapy reticulocytosis starts within 48 to 72 hours, peaking at 5-7 days.

It was found that there was a significant increase in the RBC count in the ferrous ascorbate group at the end of 12 weeks. As already mentioned, the rise in Red blood cell count is due to accelerated erythropoiesis after initiation of iron supplements.

In the current study there was a statistically significant difference among the two groups with respect to mean serum ferritin being more in ferrous ascorbate group in week 12. In a study was conducted by Azza et al, significant increase in Hb was seen in all three groups which were ferrous bisglycinate, iron multi amino acid chelate and ferrous fumarate (p<0.05). Increase in ferritin with ferrous bisglycinate was significantly more than other treatments (p<0.05). Increase in serum ferritin begins in 4-30 days after start of iron supplements and repletion of stores take about 1 to 3 months. Serum ferritin is the surrogate marker of body iron stores.

Duque et al conducted a randomized controlled trial in school children to study the effect of ferrous sulfate and iron bisglycinate chelate on ferritin concentration and found that there was significant increase in serum ferritin concentration after 90 days treatment with both the drugs and this effect persisted for 6 months after supplementation. Panicker et al, compared the efficacy and safety profile of ferric ammonium citrate, ferrous fumarate, ferrous sulphate and ferric calcium citrate. At the end of 3 months when compared to baseline significant improvement (p<0.0001) was seen in red cell indices (MCV, MCH, MCHC), hemoglobin and serum ferritin. However, there was no significant difference in red cell indices and serum ferritin in patient treated with ferric ammonium citrate, ferrous fumarate, ferrous sulphate and ferric calcium citrate at the end of treatment.

In the current study it was found that diarrhea, nausea and vomiting, constipation, and gastritis were more among the ferrous ascorbate group than the colloidal iron group. This difference was statistically significant. Cancelo-Hidalgo et al, conducted a systemic review to analyze the tolerability of several iron supplements and concluded that Ferrous sulfate with mucoproteose is the best tolerated iron preparation as it had the lowest incidence of adverse effects. A study was conducted by Azza et al found that Iron multi amino acid chelate and ferrous fumarate has side effects like nausea, vomiting, constipation, abdominal pain which were more when compared to iron bisglycinate group. But this difference was not statistically significant. Gupta et al found that side effects were maximum with ferrous sulphate (52.31%), followed by ferrous ascorbate (45%) and minimum with colloidal iron (21%). Panicker et al compared the efficacy and safety profile of ferric ammonium citrate, ferrous fumarate, ferrous sulphate and ferric calcium citrate and no significant difference was found in the efficacy and safety in between these four groups. The side effects associated with iron preparations are dose dependent. Iron can be advised to be taken with small meal to decrease the gastrointestinal side effects. The difference in safety profile between IPC and ferrous salt could be attributed to slower release of iron from the stable IPC complex.

The limitation of the study was that it was non randomized with small sample size in both the group. More multicentric randomized studies with large sample size can be conducted to establish these findings.

**CONCLUSION**

The present study concluded that the ferrous ascorbate is an efficient oral iron supplement in the treatment of iron deficiency anemia in the pediatric age group compared to colloidal iron. It was found that oral ferrous ascorbate showed significant decrease in the iron deficiency anemia over 12 weeks of consumption as compared to oral colloidal iron.

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