ORIGINAL RESEARCH

Ferrous Ascorbate: Current Clinical Place of Therapy in the Management of Iron Deficiency Anemia

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Abstract

Iron deficiency anemia (IDA) is a major public health problem in India. Iron deficiency can easily be corrected with iron supplementations. Oral iron preparations are used for mild to moderate anemia and available for the supplementation of iron including ferrous sulfate, fumarate, gluconate, glutamate, succinate, and lactate, and the reference product of ferrous ascorbate. In clinical practice, ferrous ascorbate is the most widely prescribed oral iron supplement as it has a good efficacy and is well tolerated in both adults and children. Ferrous ascorbate has a better bioavailability, as high as 67%, and utilization of iron when compared to other iron preparations, including sucrosomial iron. Ferrous ascorbate lacks food interactions and can be administered without regard to food. Ferrous ascorbate is a stable chelate that does not dissociate in the gastrointestinal tract. Higher absorption of iron from ferrous ascorbate can be explained by the ascorbate component that prevents oxidation of the iron to a ferric state. A mean rise in hemoglobin (Hb) greater than 5.0 g/dL in 60 days and greater than 2.0 g/dL within 45 days is reported with once-daily therapy of ferrous ascorbate. Ferrous ascorbate is also efficacious for the prophylaxis of anemia in patients who undergo surgical procedures. Ferrous ascorbate is more effective than ferrous sulfate or carbonyl iron for the treatment of IDA. Thus, ferrous ascorbate has an important place in the clinical management of IDA in real-life scenarios.

Keywords: Efficacy, Ferrous ascorbate, India, Iron deficiency anemia, Supplemental iron, Tolerability.

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Introduction

Anemia is a common clinical diagnosis and a huge public health problem. The World Health Organization (WHO) defines anemias as hemoglobin (Hb) below 13 g/dL for adult males, 12 g/dL for nonpregnant adult women, and 11 g/dL for pregnant women.[1,2]

Epidemiology of Anemia

According to the WHO, anemia particularly affects children and pregnant women, and 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic.[3] Iron deficiency anemia (IDA) accounts for nearly half of the global burden of anemia.[4] In India, more than 50% of women aged 15–49 years were anemic from 2015–2016.[5] The National Family Health Surveys (NFHS) from 2005–2006 and 2015–2016 by the Ministry of Health and Family Welfare, India, have shown a high prevalence of anemia among women (Table 1). As per NFHS 5 (2019–2020), district wise survey showed that the total prevalence of anemia among nonpregnant women aged 15–49 years (<12.0 g/dL) ranges from 26–93.7%, pregnant women aged 15–49 years (<11.0 g/dL) ranges from 20.9–78.1%, and all women aged 15–49 years ranges from 25.8–92.8%.[6,7]

Iron Deficiency Anemia

IDA is caused by inadequate intake or absorption of iron. Further, spurts of growth and increased physiological requirements may lead to IDA in infants, in particular premature infants, growing children, and pregnant and lactating women. Medical conditions like chronic kidney disease are associated with IDA due to excessive loss of erythrocytes during hemodialysis. During pregnancy, IDA has negative consequences for both mother and the fetus. It may lead to fatigue, pallor, palpations, preterm delivery, postpartum hemorrhage, puerperal sepsis, prolonged labor, and lactation failure in the mother, and low birth weight, growth retardation, death in utero, neonatal anemia, and increased risk of infections in the fetus.

Iron Supplementation

Oral iron supplementation is used for the treatment of mild to moderate IDA, whereas severe cases need parenteral therapy. Parenteral preparations are also preferred options for patients with intolerance to oral iron preparations or malabsorption. Oral preparations for iron supplementation should be effective and well-tolerated. Iron supplementation should be sustained over a period of 2 months or more to achieve the target Hb levels. Therefore, iron preparation with favorable tolerability to have a good compliance to the therapy is required. Response to iron supplementation is influenced by a myriad of factors, including the severity of anemia,

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Table 1: Prevalence of anemia in India

Anemia among women	*NFHS 4 (2015–2016)*			*NFHS 3 (2005–2006)*
	Urban (%)	*Rural (%)*	*Total (%)*	*Total (%)*
Nonpregnant women aged 15–49 years (<12.0 g/dL)	51.0	54.3	53.1	55.2
Pregnant women aged 15–49 years (<11.0 g/dL)	45.7	52.1	50.3	57.9
All women aged 15–49 years	50.8	54.2	53.0	55.3

NFHS, national family health surveys

presence of other medical illnesses, iron salt, its absorption, bioavailability, and most importantly tolerability.

There are several challenges in the supplementation of iron in developing countries. In India, dietary preferences are mainly vegetarian, and the culinary choices have large amounts of inhibitory ligands like phytates, phosphates, tannins, and polyphenols, which inhibit iron absorption by oxidizing ferrous iron to the ferric form.

Overview of Iron Absorption

Iron in the ferrous state is the physiological form for absorption in the intestine. Iron in the ferric is converted into insoluble ferric hydroxide that has limited absorption in the alkaline pH of the small intestine.[8] Absorption of trivalent iron in the intestinal mucosa involves the reduction of the ferric species to ferrous iron, which is transported across the membrane into the enterocytes.[9] This leads to a free radical generation. An added advantage of ferrous ascorbate is the reducing action of ascorbate that prevents cellular damage due to free radicals (Flowchart 1).

Factors Influencing Iron Absorption

The efficiency of absorption of iron depends upon the type of salt for medicinal iron, the amount administered, the dosing regimen, and the size of iron stores. Iron from supplements with ferric forms is required to be converted into ferrous forms for absorption after oral therapy.[10,11] When compared to the ferric form, the ferrous form of iron has clinical advantages. Iron III hydroxide polymaltose has a poor bioavailability (3–4 times lesser than the ferrous form), and the clinical efficacy is yet to be established.[12] Women with IDA who received oral ferric protein succinylate tablets ($n = 30$) and ferrous glycine sulfate tablets ($n = 34$) for 3 months achieved higher mean Hb (0.95 vs 2.25 g/dL) and hematocrit (2.62 vs 5.91%) with the ferrous preparation.[13]

Ferrous Salts for Oral Iron Therapy and Supplementation

Ferrous salts are traditionally recommended, and several bivalent iron salts have been used for supplementation. These include ferrous sulfate, fumarate, gluconate, glutamate, succinate, and lactate. Ferrous ascorbate is known to remain soluble in the alkaline pH of the small intestine, which is an advantage over other ferrous salts in iron supplements.[14] The ascorbate preparations of iron help to increase the utilization of iron and prevent iron overload. This is explained by the mobilization of iron from the core of ferritin to the sites of erythropoiesis and inhibition of the conversion of ferritin into hemosiderin by ascorbic acid.[14,15]

Ferrous ascorbate has comparable efficacy to ferrous sulfate that is a commonly used iron preparation in clinical practice. A study in 18 healthy phlebotomized volunteers who received a prolonged-release ferrous sulfate formulation or a quick-release ferrous ascorbate preparation showed no differences in intestinal absorption of iron measured on day 21.[16] In this study, the rise in Hb was similar after treatment for 2 months. Panchal et al. reported comparable efficacy of ferrous ascorbate with iron sulfate in patients with IDA.[10] Ferrous ascorbate is used as a reference molecule in international studies.[14,17]

Ferrous Ascorbate

Chemistry

Ferrous ascorbate is a synthetic chelate of iron in the ferrous state with ascorbic acid. The unique chemistry of ferrous ascorbate includes a high content of iron and its coexistence with ascorbate in the same compound.[18] Ascorbic acid, in quantities greater than 200 mg, increases the absorption of medicinal iron by at least 30%.[17] Ferrous ascorbate has a high iron content (12–15%) and ascorbic acid.[14]

Ferrous ascorbate has a quick response as improvement in Hb can be seen as early as 15 days after the initiation of supplementation with ferrous ascorbate.[15] The evident good efficacy and excellent safety and tolerability of ferrous ascorbate can be explained by advantages of the chemical state including a better bioavailability and utilization of iron.

The chemical state of ferrous iron in oral supplements has a distinct advantage over iron in the ferric form. Given the high effectiveness, acceptable tolerability, and low cost of ferrous preparations, these are preferred over ferric preparations of oral iron supplementation.[13]

Pharmacokinetics

Iron in conventional ferrous salts is subject to oxidation by the alkaline milieu in the gastrointestinal tract and by food constituents. In the ascorbate preparation, iron is maximally absorbed due to: (i) Inhibition of conversion of ferrous into ferric iron, leading to better absorption, (ii) inhibition of the effect of phytates, phosphates, and oxalates on iron absorption, and (iii) inhibition of formation of insoluble iron complexes that interfere with absorption.[15,19] Ferrous ascorbate has some inherent features that facilitate its absorption. Ferrous ascorbate dissociates to monomeric cations in aqueous solutions. Between pH of 6 and 8, ferrous ascorbate shows a solubility-enhancing effect of ascorbate.[20] Some distinctive manufacturing process including advanced coating technology (ACT) adds stability to the ferrous ascorbate chelate and prevents it from dissociating in the presence of inhibitors in the stomach leading to higher absorption (data on file).

Bioavailability

Ferrous ascorbate has a high bioavailability. In a study in 45 healthy males, the National Institute of Nutrition, Hyderabad, reported absorption of 8.3, 6.3, and 0% iron from ferric orthophosphate, sodium iron pyrophosphate, and ferric pyrophosphate, respectively, and 30.6% from ferrous ascorbate.[21] Several studies have reported a similarly high absorption (39–43.7%) of iron from ferrous ascorbate and absorption as high as 67% is reported in the state of iron

Flowchart 1: Intestinal absorption of ferric and ferrous forms of oral iron

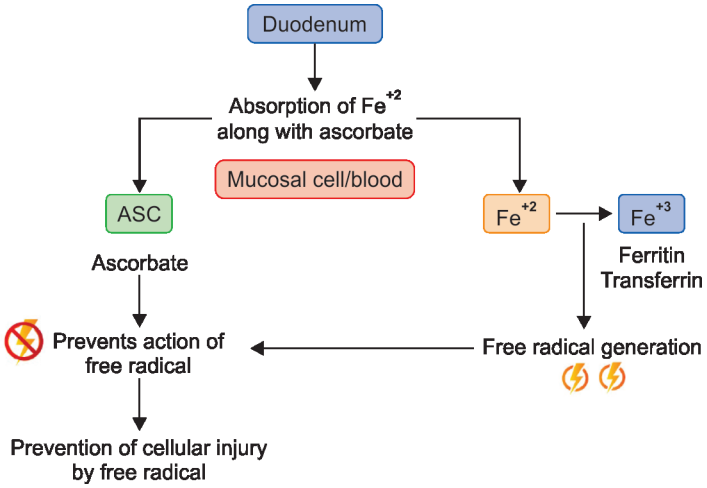

Table 2: Reported absorption of elemental iron from various iron preparations

Iron preparation	*Absorption (%)*
Ferrous ascorbate	67
Ferrous sulfate	7.7–10.9
Iron polymaltose	8.8
Ferric ammonium citrate	2.4
Ferric hydroxide	2.4
Ferric orthophosphate	8.3
Sodium iron pyrophosphate	6.3
Ferric pyrophosphate	0
Ferrous fumarate	3–6.3
Ferrous bisglycinate	6–9.1
Ferrous gluconate	Less than or equal to ferrous sulfate
Carbonyl iron	70% of ferrous sulfate

deficiency with anemia.[22,23] In a bioavailability assessment of iron compounds, the geometric mean absorption from ferrous sulfate, ferrous ammonium phosphate, and ferric pyrophosphate was 10.4, 7.4, and 3.3%, respectively.[24] The greater absorption of iron from ferrous ascorbate when compared to ferrous sulfate is explained by the prevention or retardation of oxidation of ferrous iron by ascorbate and the existence of ferrous iron as a chelate with ascorbate.

In a comparative study for ferric and ferrous preparations of oral iron, there was a significant difference in the bioavailability of 59Fe III hydroxide polymaltose compared to that of 59Fe labeled-bivalent iron preparations like ferrous ascorbate or a quick-release ferrous sulfate. Intestinal iron absorption in the fasting state was low for the Fe III complex (1.2 ± 0.1%) as compared to ferrous ascorbate (43.7 ± 7.1%). After a meal, the absorption of the ferrous preparation was not affected, whereas that of the ferric preparation increased to 8.8 ± 4.7%. After an equivalent therapeutic dose of 100 mg elemental iron over 28 days, daily rise in Hb concentration was greater for the ferrous preparations (1.1 ± 0.3 g/L) compared to the Fe III hydroxide-polymaltose complex (0.68 ± 0.2 g/L).[24,25] Only about 1–8% of iron is absorbed from the available preparations of oral iron.[2] Table 2 shows the extent of absorption of elemental iron from various iron preparations.[23,26–31]

Regardless of the iron status, ferrous ascorbate has the highest percent uptake when compared to the uptake from other forms of iron. Yeung et al. compared the iron uptake from radiolabeled ferrous sulfate, ferrous ascorbate, ferrous bisglycinate, ferric chloride, ferric citrate, and ferric EDTA by Caco-2 cells with different iron status to mimic iron-deficient and iron overload and in the presence of divalent metal cations. When compared to cells receiving no supplemental iron, cells receiving supplemental iron showed significant reductions in uptake from radiolabeled ferrous ascorbate and ferrous bisglycinate, but not from ferric compounds. Ferrous ascorbate had the greatest percent reduction (−90%).[32] Ferrous form of the iron has the highest absorption efficiency.

Efficacy of Ferrous Ascorbate

Ferrous ascorbate is widely used in clinical practice. In a retrospective analysis of hospital records of 250 patients with anemia (15–35 years of age) being treated in a teaching hospital in India, ferrous ascorbate was most commonly prescribed (69.2%), followed by ferrous sulfate (13.6%), ferrous fumarate (9.6%), and ferric ammonium citrate (7.6%).[19]

Ferrous ascorbate has shown good efficacy in an open-label, prospective study in clinical settings in India (Table 2).[15] Oral once daily administration of a fixed-dose combination tablet (Orofer-XT) of ferrous ascorbate (equivalent to 100 mg iron) and folic acid (1.1 mg) for 45 days showed a rapid rise in Hb (mean: 2.37 g/ dL; 95% CI: 2.25–2.49) in 1,461 women (IDA without pregnancy: 508; anemia during pregnancy: 613; pregnancy with IDA: 204; not specified: 136) who had a mean baseline Hb of 8.53 ± 1.46 g/dL (95% CI: 8.45–8.61) and mean age of 27 ± 8 years. In this study, ferrous ascorbate was well tolerated, and a significant improvement in Hb was reported as early as 15 days (mean: 1.67; 95% CI: 1.56–1.78). The largest rise in Hb (3.60 g/dL) was seen in women with Hb less than 6 g/dL at baseline followed by those with baseline Hb of 6–8 g/dL (2.91 g/dL), 8.1–10 g/dL (2.23 g/dL), and greater than 10 g/dL (1.25 g/dL). In addition, there was a marked improvement in fatigue and pallor.

In an open-labeled, randomized study, ferrous ascorbate ($n = 30$) was compared to carbonyl iron ($n = 30$) for IDA (Table 3).[33] Patients received the two preparations in doses equivalent to 100 mg elemental iron for 60 days. The mean rise in hemoglobin

Table 3: Key studies for ferrous ascorbate in IDA

Parameter	*HERS study*	*PRIDE study*
Sample size	1,461 women	60 men and women
Study design	Open-label prospective study	Open label, randomized, prospective study
Study duration	45 days	60 days
Mean ± SD age (years)	27 ± 8	FA: 34 ± 10.75 CI: 34.35 ± 12.13
Baseline Hb (g/dL)	8.08 ± 1.38	FA: 6.94 ± 1.67 CI: 7.16 ± 1.62
Oral iron therapy (once daily)	Orofer-XT tablet: Fixed-dose combination of ferrous ascorbate (equivalent to 100 mg of elemental iron) and 1.1 mg folic acid	Orofer-XT tablet (one tablet): Fixed-dose combination of ferrous ascorbate (equivalent to 100 mg of elemental iron) and 1.1 mg folic acid OR Fefol-Z capsule (two capsules): Fixed-dose combination of carbonyl iron (equivalent to 50 mg of elemental iron), zinc sulfate monohydrate (equivalent to 22.5 mg of elemental zinc), and 0.5 mg of folic acid
Hb at follow-up	10.72 ± 1.42	FA: 11.97 ± 1.09 CI: 9.99 ± 1.47
Hb rise in subgroups of anemia*		
<6 g/dL	3.60 (3.07–4.13)	FA: 6.83 ± 1.74; CI: 3.44 ± 0.953 ($p = 0.0001$)
6–8 g/dL	2.91 (2.75–3.07)	FA: 4.59 ± 1.18; CI: 3.22 ± 1.93 ($p = 0.0761$)
8.1–10 g/dL	2.23 (2.11–2.35)	FA: 3.67 ± 0.55; CI: 1.81 ± 0.47 ($p < 0.0001$)
>10 g/dL	1.25 (1.05–1.45)	Not reported
Safety	Most common GI adverse events were nausea, gastritis, acidity, loose motions, and black stool	GI adverse events probably not related to therapy

CI, carbonyl iron; FA, ferrous ascorbate; GI, gastrointestinal; Hb, Hemoglobin; SD, standard deviation; *Subgroups in the PRIDE study were ≤6 g/dL, 6.1–8 g/dL, and 8.1–9.9 g/dL

was significantly greater with ferrous ascorbate (5.03 ± 1.81 g/dL) than with carbonyl iron (2.82 ± 1.43 g/dL). The responder rate was higher with ferrous ascorbate as 93.33% patients were rendered nonanemic as compared to 46.66% by carbonyl iron [absolute risk reduction:46.67%; (99% CI = 17–76.2%); relative risk reduction: 88%; number needed to treat: 2.1]. The rise in serum ferritin was better with ferrous ascorbate (53.20 ± 13.35 vs 38.22 ± 15.21 µg/L; $p = 0.0002$).

Ferrous ascorbate has also been used in the prophylaxis of anemia in surgical patients. In a prospective study in 68 patients who underwent orthopedic surgery and autotransfusion, prophylaxis with ferrous ascorbate (99 mg elementary iron) starting 1 week before their first blood donation and up to 2 months after surgery restored Hb levels and ferritin levels.[34]

Comparison of Ferrous Ascorbate with Other Oral Iron Preparations

When compared to other iron salts, ferrous ascorbate has been shown to have better efficacy in children. In a comparative study of ferrous ascorbate and iron polymaltose complex (IPC) (dose of 6 mg/kg) for the treatment of IDA in children, there was a significant improvement in Hb at 12 weeks compared to baseline in both the groups. The rise in Hb was 4.88 + 1.28 g/dL and 3.33 + 1.33 g/dL with ferrous ascorbate and IPC, respectively, and the improvement in Hb was significantly higher for ferrous ascorbate ($p < 0.001$).[35] There is mixed evidence for the efficacy of IPC in the treatment of IDA. Some studies report its efficacy for raising Hb to be as good as ferrous sulfate or other salts[36,37], and others report no significant differences.[38]

Better efficacy has been reported for ferrous ascorbate compared to colloidal iron preparation. In an open-labeled, randomized, parallel-group comparison of ferrous ascorbate ($n = 41$) and colloidal iron ($n = 39$) in children (6 months to 12 years in age) with IDA (Hb <10 g%), ferrous ascorbate resulted in a significantly higher rise in Hb at 12 weeks when compared to colloidal iron (3.24 ± 1.66 g% vs 1.42 ± 2.04 g%; $p < 0.01$).[39] In this study, children received elemental iron in doses of 3 mg/kg/day for 12 weeks. Responder rate (Hb ≥ 11.5 g%) after 12 weeks of therapy was also significantly higher for ferrous ascorbate (53.57 vs 10.34%; $p < 0.01$). In another study, mean rise in Hb was higher with ferrous ascorbate (daily dose of 3 mg/kg) than with colloidal iron at 12 weeks (3.59 ± 1.67 vs 2.43 ± 1.73 g/dL; $p < 0.01$).[40]

In an open-label, randomized, comparative study of ferrous ascorbate ($n = 30$) and carbonyl iron ($n = 30$) in the treatment of IDA, ferrous ascorbate showed a significantly ($p < 0.05$) greater increase in Hb (5.03 ± 1.81 vs 2.82 ± 1.43 g/dL above baseline).[33]

Ferrous ascorbate is more effective than ferrous sulfate for the treatment of IDA. In a prospective, randomized, comparative clinical study, Singhal et al. reported a significant and comparable rise in Hb on days 30 and 60 with ferrous sulfate (100 mg), fumarate (100 mg), ascorbate (100 mg), sodium feredetate (33 mg), and ferrous bisglycinate (30 mg) in the treatment of IDA in 250 antenatal women with Hb between 7 and 10 g%.[40,41] At day 60, the rise in Hb was significantly more with ferrous ascorbate (1.13 ± 0.35; $p = 0.024$) and ferrous bisglycinate (1.11 ± 0.27; $p = 0.014$) as compared to ferrous sulfate.

Newer generation iron preparations, such as sucrosomial, are currently available. These preparations are said to have a higher

absorption rate, better tolerability, better compliance, and better clinical outcomes. It may be noteworthy that these preparations are currently approved for food supplementation in India and contain only 30 mg of elemental iron. This sets in limitations for therapeutic use in the management of IDA. There are no data from human studies to support the high bioavailability of sucrosomial iron. These preparations have limited clinical evidence, and most of the studies have a small sample size. One study has reported a rise in Hb with 120 mg dose and at expense of gastrointestinal side effects in 26% of patients.[42] Published evidence highlighted that frequency and number of pills can lead to noncompliance with iron deficiency treatment that may be critical in the management of IDA.[43] Similarly, multiple daily dosing of sucrosomial iron may adversely impact compliance with therapy.

Safety of Ferrous Ascorbate

Safety is a key concern in oral iron supplementation as up to 50% of patients develop gastrointestinal adverse events that lead to reduced compliance.[42] The tolerability of oral iron supplementation is influenced by factors such as age, body mass, and genetic variants for tolerance in the patient.[19] Ferrous ascorbate has a good safety profile and tolerability. Ferrous ascorbate delivers the maximum amount of ferrous iron to the duodenal brush border and reduces possible gastrointestinal adverse events.[15]

In a real-world experience, ferrous ascorbate was well tolerated in 1,461 pregnant and nonpregnant women. Gastrointestinal AEs were reported in 7.05% (95% CI: 5.79–8.49%) of women, which included acidity, loose stools, constipation, gastritis, nausea, vomiting, and black stools.[15] In general, gastrointestinal upset with iron supplemental preparations is minimal if the daily doses do not exceed 180 mg elemental iron and when given with food.[18]

Ferrous ascorbate is also well-tolerated in children. In a comparative study of ferrous ascorbate and colloidal iron supplementation in doses of 3 mg/kg/day for 12 weeks in 80 children aged 6 months to 12 years, ferrous ascorbate was well accepted and there were no reported side effects.[39]

In a comparative evaluation of ferrous sulfate (100 mg), fumarate (100 mg), ascorbate (100 mg), sodium feredetate (33 mg), and ferrous bisglycinate (30 mg) in antenatal women, maximum side effects were reported with ferrous fumarate (51 AEs) followed by ferrous sulfate (40 AEs), ferrous bisglycinate (26 AEs), ascorbate (18 AEs), and sodium feredetate (10 AEs).[40] None of the iron preparations were associated with treatment discontinuations.

It is important to note total Indian patient exposure of ferrous ascorbate (Orofer-XT) is 1849293 patient-treatment-year (data on file).

Expert Opinion

Anemia continues to be a global public health issue and needs attention specifically in the low- and middle-income countries, and iron deficiency is a primary cause of anemia.[44] Anemia affects overall well-being and has long-term adverse effects. Anemia is an important public health problem in India as almost 53% of women and 23% of men in the age-group of 15–49 years are anemic. Anemia affects all the age-groups; 59% of children of age less than 5 years are anemic. Similarly, almost half of the pregnant females are anemic.[6] About 85% of postmenopausal women in India are anemic.[45]

Therefore, prompt iron supplementation for correcting IDA is important and critical. Ferrous ascorbate is a preferred oral iron preparation for the prevention and treatment of IDA in pregnant women, children, and the general population. Ferrous ascorbate offers significant clinical advantages such as high bioavailability of 67%, quick response, good efficacy, safety, and tolerability. Many studies for iron preparations are performed with ferrous ascorbate as a reference molecule. A unique advantage of ferrous ascorbate is the presence of both ferrous iron and ascorbate in a single compound. Regardless of iron status, ferrous ascorbate has the highest uptake when compared to other iron supplement options. The rapid response to oral supplementation with ferrous ascorbate with improvement in Hb can be seen as early as 15 days after the initiation of supplementation, and a mean rise in Hb greater than 5.0 g/dL in 60 days and greater than 2.0 g/dL within 45 days is reported with once-daily oral therapy of ferrous ascorbate. Patients with lower baseline Hb have a maximum increase in Hb following oral treatment with ferrous ascorbate.[15] The usual recommended dose of iron during pregnancy is 100 mg daily.[46] The products of ferrous ascorbate having ACT and huge patient exposure had an important relevance in clinical practice.

Any iron preparations approved as food supplementation contain a lower concentration of iron and have limited clinical evidence and should best be avoided for the treatment of IDA.

Thus, iron supplementation is important for the management of IDA. The right selection of iron preparation is very critical to get the maximum benefits in the patients. Ferrous ascorbate can help to combat the huge burden of anemia by providing an effective option to synthesize and restore Hb as iron deficiency is the most common cause of nutritional anemia worldwide.[7] Present evidence highlights that ferrous ascorbate with high absorption rates that translated in a rapid and clinically meaningful increase in Hb, and favorable tolerability makes it the preferred iron preparation in the management of IDA.

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