Managing anemia: Focus on ferrous ascorbate and folic acid

INTRODUCTION
Anemia is a common medical problem, especially in females, and is associated with an increased mortality and morbidity risk and a reduced quality of life. Consumption of iron ameliorates iron deficiency, the most prevalent nutritional deficiency in the world, affecting approximately 2 billion persons. Consumption of adequate amounts of folic acid by women before pregnancy and during early pregnancy decreases their risk for having a pregnancy affected by neural tube defects (NTDs), the most common preventable type of birth defects worldwide.

CLASSIFICATION OF ANEMIA
The classification of anemia is usually based on the average erythrocyte size, referred to as the mean corpuscular volume (MCV). Microcytosis indicates a reduced haemoglobin synthesis caused by either an iron deficiency or haemoglobinopathy, a congenital disorder. Macrocytosis is the result of a disruption to the division and maturing of proerythroblasts in the bone marrow, due, for example, to vitamin B₁₂ or folic acid deficiency or excessive alcohol use. Furthermore, a high number of reticulocytes in the blood indicates an increased production of erythrocytes whereas a low total indicates an inadequate production level.

Serum ferritin determination remains the most accurate laboratory test for the diagnosis of iron deficiency anemia and its differential diagnosis with the anemia of chronic disease. Although erythropoietin analysis has no clear diagnostic value at the moment, it has become more and more obvious that its therapeutic importance in elderly patients with chronic anemia is increasing.¹

CHRONIC SEVERE ANEMIA SEEN IN OBSTETRIC PATIENTS IN NORTH INDIA
In a study done, of 5124 deliveries during January to December 2000, 386 patients (7.53%) were severely anemic (Hb < 6.0 g/dl). 1083 units of blood were transfused to these patients, a mean of 2.80 units to each patient. There were 2 maternal deaths due to severe anemia. It was concluded that along with prophylaxis with iron and folic acid sufficient consideration should be given to sanitation facilities, safe drinking water, recurrent gastrointestinal infection etc.²

The effect of iron deficiency on serum levels of transferrin, iron and ferritin

The increase in serum transferrin level along with a fall in serum iron level lowers the transferrin saturation (serum iron level divided by the serum transferrin level.)
NUTRITIONAL ANEMIA AND ITS CONTROL IN INDIA
Available studies on prevalence of nutritional anemia in India show that 65% of infants and toddlers, 60% of 1-6 years of age, 88% adolescent girls (3.3% had hemoglobin < 7.0 g/dl; severe anemia) and 85% pregnant women (9.9% having severe anemia) were anemic. The prevalence was marginally higher in lactating women as compared to pregnancy. The commonest is iron deficiency anemia. National programmes to control and prevent anemia have not been successful. Experiences from other countries in controlling moderately-severe anemia guide to adopt long-term measures i.e. fortification of food items like milk, cereal, sugar, salt with iron.

As an immediate measure medicinal iron is necessary to control anemia. Addition of folate with iron controls anemia and is neuroprotective. Evidence in early childhood suggests vitamin B12 deficiency anemia; thus it may also be given along with iron and folate.

ASCORBIC ACID
The effect of ascorbic acid on iron retention from a diet with predicted low iron bioavailability (containing minimal meat and ascorbic acid) was investigated in iron-depleted premenopausal women. Eleven women were depleted of storage iron (indicated by serum ferritin) through a combination of diet (5.0 mg Fe/2000 kcal for 67-88 d) and phlebotomy. They then consumed a diet containing 13.7 mg Fe/2000 kcal, supplemented with placebo or ascorbic acid three times daily (1500 mg total) with meals for 5.5 wk. Ascorbic acid improved apparent iron absorption (balance method) [38 ± 2% (means ± SEM) vs 27 ± 2%]. Ascorbic acid also improved hemoglobin, erythrocyte protoporphyrins, and serum iron but not hematocrit, serum ferritin, iron-binding capacity, or transferrin saturation. In iron-depleted women consuming a diet with predicted poor iron availability, ascorbic acid supplementation enhanced body iron retention for 5.5 wk.

EFFECT OF ASCORBIC ACID ON IRON ABSORPTION
The effect of ascorbic acid on the absorption of non-heme iron was studied in 299 subjects. Different meals in which the non-heme iron was labelled with two different radio-iron isotopes were served with and without ascorbic acid to the same subject. Other meals containing foods with a known high content of ascorbic acid were also studied.

Studies were also made giving different amounts of ascorbic acid with different meals. Marked differences in the enhancement of iron absorption were seen when ascorbic acid was given in different meals. Results show that ascorbic acid has a key role in facilitating the absorption of non-heme iron from the diet and that about 50 mg of the vitamin in each main meal is desirable for optimum effect.

ADVANTAGES OF FERROUS ASCORBATE OVER CONVENTIONAL IRON THERAPY
Ferrous ascorbate has the advantage of providing both ferrous iron and ascorbate in the same compound. The greater absorption of iron in vivo from ferrous ascorbate as compared with ferrous sulfate has been ascribed both to retardation or prevention of Fe(II) oxidation by ascorbate and to the existence of Fe(II) as a chelate with ascorbate. The available literature and our own results demonstrate that ferrous ascorbate dissociates in aqueous solution into a monomeric cationic species i.e it is almost completely dissociated, so (chelate) complex formation does not contribute significantly to the increased iron absorption. Between pH = 6 and pH = 8 a solubility enhancing effect of ascorbate is observed which is of relevance for the iron absorption from ferrous ascorbate.

DIFFERENT IRON UPTAKE FROM RADIOLABELLED IRON SOURCES
Iron uptake from radiolabeled ferrous sulfate, ferrous ascorbate, ferrous bis-glycinate, ferric chloride, ferric citrate and ferric EDTA by Caco-2 cells with different iron status, and in the presence of divalent metal cations, was compared. The iron status of the cells were altered to produce iron-deficient and iron-overloaded cells and thereby mimic absorption from iron-deficient and iron-overloaded humans.

In cells receiving supplemental iron, there were significant decreases in uptake from radiolabeled ferrous ascorbate and ferrous bis-glycinate, but not from ferric compounds, when compared to cells receiving no supplemental iron. The inhibition was more pronounced in ferrous iron uptake than ferric iron uptake, with ferrous ascorbate

Drug      Composition                                      Packing   Administration
IROCAFE XT Ferrous Ascorbate 500 mg, eq.to Elemental Iron 100 mg, Folic Acid IP 1.5 mg, Excipients Q.S. 10 Tablets   1 BD
showing the greatest percent reduction (-90%).

Regardless of the iron status, ferrous ascorbate showed the highest percent uptake, followed by ferrous bis-glycinate, whereas uptake from all other forms of iron was significantly lower.7

**RESPONSE TO FERROUS ASCORBATE PROPHYLAXIS IN SURGERY**

In order to evaluate the response to prophylactic ferrous ascorbate, a prospective study was conducted on patients subjected to orthopaedic surgery and autotransfusion. Starting one week before their first blood donation and up to 2 months after surgery, each patient received 99 mg elemental iron per days as oral ferrous ascorbate.

Haemoglobin rates decreased in every control, returning to values close to the initial ones by the end of the programme (mean figures are as follows: 14.63; 13.17; 12.70; 11.88; 14.11 g/dL); and similar changes were seen with respect to the other parameters of blood. The initial and final values for ferritin were 157.32 and 91.06 ng/mL, respectively, and no significant changes were appreciated in the other data from the iron profile, regardless of the number of blood units collected in a given case. Recombinant erythropoietin is more expensive a method. Ferrous ascorbate is better tolerated than ferrous sulphate plus additives.8

**FOLATE**

Folate is a water-soluble vitamin of the B complex group, and is required for optimal health, growth, and development. In humans, it cannot be synthesized de novo. As a cofactor or coenzyme, folate plays key biological roles in a variety of physiologic processes: maintenance and repair of the genome, regulation of gene expression, amino-acid metabolism, neurotransmitter synthesis, and the formation of myelin.

**HIGHLIGHTS**

- Nutrition education to improve dietary intakes in family for receiving needed macro/micro nutrients as protein, iron and vitamins like folic acid for hemoglobin synthesis is important.
- In iron-depleted women a diet with predicted poor iron availability, ascorbic acid supplementation enhanced body iron retention. Ascorbic acid promotes iron absorption from the diet by reducing the negative effect on iron absorption of certain ligands such as phytates and tannins present in the diet. Crystalline ascorbic acid and native ascorbic acid in foods appeared to have the same effect in promoting absorption of iron.
- In a study regardless of the iron status, ferrous ascorbate showed the highest percent uptake, followed by ferrous bis-glycinate, whereas uptake from all other forms of iron was significantly lower. Recombinant erythropoietin is more expensive whereas ferrous ascorbate is better tolerated than ferrous sulphate plus additives.
- A meta-analysis of randomized trials of folic acid for the prevention of recurrent NTDs indicates a 69% reduction in recurrence risk if analyzed on an intention-to-treat basis and an 87% reduction among those women who took supplements prior to the beginning of pregnancy.

**REFERENCES**

✓ Ferrous ascorbate, a synthetic molecule of ascorbic acid and iron, is indicated in the treatment of iron deficiency anemia.

✓ Ferrous Ascorbate is the world’s most widely recognized reference iron

✓ Designed for Better Performance

✓ Enhanced Iron Absorption

✓ Faster Haemoglobin Rise

✓ Devoid of the side effects of conventional Iron

The greater absorption of iron in vivo from ferrous ascorbate [Fe(HL)2] as compared with ferrous sulfate has been ascribed both to retardation or prevention of Fe(II) oxidation by ascorbate and to the existence of Fe(II) as a chelate with ascorbate.