REVIEW ARTICLE

Iron Deficiency Anemia : Management and Prevention in Children

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Introduction

Iron deficiency anemia (IDA), a major health problem in children with serious consequences, is of great public health importance. Incidence of IDA in India is at the explosion level and its prevention and treatment require less share of medical budget(1). Over the last 50 years, the prevalence of iron deficiency anemia has ranged between 68 to 97 percent in children(2-6). Infants, toddlers, prescholars and adolescents are at a great risk of developing IDA.

Much of the IDA is the fallout of anemia in pregnant women resulting in low birth weight babies and enhanced perinatal and infant mortality and morbidity(7). It is an enigma that iron deficiency should occur when man is surrounded by abundant iron on the earth. An adult male and female has approximately 4 grams and 3 grams of total body iron, respectively, which is equivalent to a small iron nail. Seventy percent of body iron is in the form of hemoglobin and rest as body storage iron, myoglobin and other iron dependent cellular enzymes (catalase, peroxidase, cytochromes and ribonucleotide reductase). A child has approximately 70 mg/ kg of body iron(6).

The therapeutic use of iron was mentioned in Greek mythology where impotence was cured by drinking iron rust dissolved in wine(8).

The purpose of this review is to provide an update about the recent developments that have occurred in management and prevention of IDA. Only recently, we have published a review on etiology and diagnosis of IDA in children(9).

Management

The management of iron deficiency anemia is considered in two parts :

(a) Treatment of the individual patient.

(b) Treatment at public health level.

The successful management requires :

(i) Confirmation of the diagnosis

(ii) Thorough investigations to find out the etiology and to treat the cause

(iii) Supplementation of iron.

Treatment of Cause

It is important to find out the etiological factor for iron deficiency, to prevent failure of therapy and recurrence of deficiency after treatment is stopped especially in older children who are likely to have a secondary IDA, as dietary deficiency is less likely at this age. Infants usually have

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poor dietary history especially lack of breast feed and improper weaning and or bottle feeding and poor intake of iron containing food as a cause of iron deficiency. Promotion of exclusive breast feeding for first 4 to 6 months, continuing breast feeding for as long as possible, thereafter with introduction of proper and age appropriate food items and prophylactic iron supplementation will prevent iron deficiency during infancy and early childhood. In older children diet modifications to improve total calorie intake and iron containing foods in diet will prevent iron deficiency. Treatment of worms, giardiasis, bleeding from any site, recurrent infections is must to treat the patient adequately besides iron.

Iron Supplementation

Iron can be given orally or parenterally.

Oral Iron Therapy

Oral iron therapy is cost effective, safe, convenient, well tolerated, preferred and advocated route of therapy.

It is given in the dose of 6 mg/kg of elemental iron in 2-3 divided doses. In one study, the initial dose of oral iron of 3 mg/ kg/ day was also tried and later on increased to 6 mg/kg/ day when infants tolerated it (10). It is preferably given empty stomach or in between meals to facilitate better absorption. Doses higher than this are not recommended as the effect is not better but side effects are much more. Compliance in the first month of therapy is important as majority of iron absorption occurs during this period. It is continued for at least 2-3 months after hemoglobin becomes normal, to replenish stores(6).

Types of Iron Salts

Various types of iron salts available are shown in Table 1. Of these ferrous salts are preferred as they are better absorbed than ferric forms. Ferrous sulfate is the best as it is also cost-effective.

TABLE 1

Percentage of Elemental Iron in various Iron Salts (1)

Iron Salts	Percentage of elemental iron
Ferrous sulphate, anhydrous	37
Ferrous sulphate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous fructose	25
Ferrous succinate	23
Ferrous lactate	19
Ferrous carbonate	16
Ferrous glycine citrate	23
Iron choline	12
Ferric sulphate	27
Ferric ammonium citrate	18
Colloidal iron	50

Iron Formulations

There are two types of iron compounds available i.e. ionic (ferrous sulfate, fumarate, gluconate etc.) and non-ionic (iron polymaltose complex and sucrose complex). Various forms of preparations are available including tablets, capsules, drops, syrups, sugar coated tablets, enteric coated tablets, slow release tablets and chewable tablets.

(a) Uncoated tablets and sugar coated tablets are the least expensive formulations and disintegrate well in the stomach. However, they become oxidized overtime and hence lose efficacy especially in humid climate.

(b) Enteric coated tablets are somewhat more expensive. They have the added drawback that they disintegrate only partially when exposed to gastric juices. Only those which disintegrate in vitro 0.1 N hydrochloric acid within two hours should be used, thus allowing slow release of iron in the stomach. The rationale for slow release is that the iron absorption is related to the amount of iron present in the duodenum and jejunum while the frequency of gastro-intestinal side effects is directly proportionate to the amount. Hence, a smaller amount of iron at a time (as compared to plain tablets) leads to fewer side effects with same efficacy.

(c) Liquid preparations are in the form of syrups and drops. These are expensive and deteriorate on

storage, but are useful for administration to infants and children who cannot swallow tablets. They usually lead to temporary staining of teeth and tongue which disappears on discontinuation of the drug.

(d) Combination with other nutrients : Incorporation of ascorbic acid, vitamins and folic acid with iron increases the cost as well increases frequency of side effects and thus risk of non-compliance.

Absorption of oral iron is enhanced by the presence of orange juice, meat, poultry products and inhibited by cereals, tea and milk.

Response to Treatment

Erythropoietic activity following iron administration is directly related to the severity of anemia. A positive response is considered when there is daily rise in the hemoglobin concentration of 0.1 g/dl from fourth day onwards. Sequence of events after iron therapy in IDA are depicted in Table 2.

TABLE 2

Sequence of events after iron therapy in IDA(11)

Time after iron administration	Development
12 - 24 hr.	Replacement of intracellular iron enzymes, subjective improvement, decreased irritability and increased appetite.
36 - 48 hr.	Initial bone marrow response, erythroid hyperplasia.
48 - 72 hr.	Reticulocytosis peaking at 5 - 7 days
4 - 30 days	Increase in hemoglobin level
1 - 3 months	Repletion of stores

Pica, pagophagia and non-specific symptoms disappear within one week. Of the epithelial lesions, those affecting tongue and nails are most responsive to treatment. After 1-2 weeks of therapy, small filiform papillae are seen on the tongue. By 3 month, the tongue is usually normal. Koilonychia usually disappears within 3-6 months.

Side Effects

Major side effects of oral iron administration include heartburn, nausea, vomiting, abdominal cramps, diarrhoea, constipation, staining of tongue and teeth, blackish discoloration of stools etc. Rarely, cases of acute iron poisoning can occur by taking accidental or suicidal overdose. By and large the side effects are less and well tolerated if proper counselling is done before starting the therapy. Of late, people have tried twice a week therapy which has proved to be equally effective if no better, with less side effects(6). Death has been reported after ingestion of as little as 650 mg of elemental iron. Absorption of 60 mg/ kg is probably necessary for development of significant iron poisoning (14).

Suboptimal response may be due to the following (6)

(1) Wrong diagnosis — It could be thalassemia minor and not IDA.
(2) Poor compliance with full course which is a major problem in our country.
(3) Discontinuation of treatment after initial 3 to 4 weeks because of feeling of well being and disappearance of symptoms of anemia.
(4) Selection of a preparation with poor absorption of iron.
(5) Adverse symptoms such as constipation, diarrhoea, heartburn and abdominal cramps.
(6) Malabsorption due to gastrointestinal diseases.
(7) Loss at a greater rate can be compensated by oral iron as in chronic bleeding.

True intolerance, genuine gastrointestinal malabsorption and excessive blood losses are only indications to resort to parentral route. Fortunately, these causes are rare in children.

Parentral Iron Therapy

This includes both intramuscular and intravenous iron therapy. This therapy is somewhat more expensive and risky than oral with same recovery rate. Total dose of iron is calculated as (15).

Total dose of elemental iron (mg) = Weight of the child (kg) x Hemoglobin deficit (g/ dl) x 4

(i) **Intramuscular preparations :** Iron dextran complex and iron sorbitol containing 50 mg of elementral iron per ml are two available forms. These are given deep into upper outer quadrant of the buttock and the skin should be laterally displaced before injection (Z track technique) to prevent staining of the skin. The dose of injectable iron is 1.5 mg (0.03 ml)/ kg/ dose (15).

(ii) **Intravenous :** There are two methods : (a) infusion of total dose diluted in ratio of 5 ml of iron dextran complex in 100 ml of normal saline. Initially flow rate should be kept at 20 drops/ min for 5-10 minutes and if there are no adverse reactions, then rate can be increased, (b) bolus injection of iron dextran diluted in 20 ml of normal saline can be given over 10 to 20 minutes. Prior to administration, sensitivity test and with a small dose should be performed.

Side effects include local pain, flushing, pyrexia, malaise, vomiting, chills, arthralgia and anaphylaxis. Tender regional lymphadenitis and myalgias are delayed side effects.

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is indicated only when the anemia is very severe or when superimposed infection may interfere with the response. It is not necessary to attempt rapid correction of severe anemia by transfusion. The procedure may be dangerous because of associated hypervolemia and cardiac dilatation. Packed or sedimented RBCs should be administered slowly in an amount sufficient to raise the hemoglobin to a safe level at which the response to iron therapy can be awaited. In generally, severely anemic children with hemoglobin values less than 4g/ dl should be given only 2-3 ml/ kg packed cells at any one time (furosemide may also be administered as a diuretic). If there is evidence of frank congestive heart failure a modified exchange transfusion using fresh packed RBCs should be considered although diuretics followed by slow infusion of packed RBCs may suffice(11).

Prevention (16,17)

There are various approaches undertaken to prevent IDA, both at individual level and at the community level. They include diet modifications, iron supplementation, food fortification and control of recurrent infections.

Diet Modification

During infancy, exclusive breastfeeding for the first 4-6 months of age will protect the baby from iron deficiency. Thereafter breastfeeding must be continued for as long as 1.5-2 years. Equally important is the introduction of iron containing age appropriate food items. Similarly preschool, school going children, adolescents and pregnant and lactating women should be encouraged to take iron rich food. In case breast milk is not available, iron fortified formula can be a better alternative than cow's milk provided one can afford it and prepare it properly and hygienically. Bottlefeeding should be discouraged and strongly condemned by all means. Prolonged breastfeeding beyond 2 years especially without introduction of age appropriate food can also lead to iron deficiency in children.

One can also increase the iron content of food by giving adequate calories in diet which itself will increase the iron content by 25-30 percent. One can encourage consumption of iron rich food like green leafy vegetables, spinach, jaggery and heme iron containing food like meat and fish. Heme iron is better available and also increases absorption of non-heme iron. Lastly, one can increase absorption of iron by adding Vitamin C containing food and by avoiding inhibitors like phytates and tannin (present in tea). Hence avoiding tea after meals and instead, consuming a portion of Vitamin C containing citrus fruit after meals is a good custom.

Control of Infections

Iron deficiency anemia and infections are inter-linked. Recurrent infections can lead to anemia of chronic infections adding to the burden of iron deficiency anemia. Hence, infections should be treated energetically. Breastmilk is the first vaccine against infection in an infant especially for decreasing morbidity and mortality due to diarrhoea and Acute Respiratory Infections(ARI).

Immunizations, sanitation and other public health measures will also help to decrease incidence of infections.

Ancylostomiasis, trichuriasis and schistosomiasis can lead to GI bleed and iron deficiency. Giardiasis can also lead to malabsorption. All these infections should be treated in time to prevent iron deficiency.

Iron Supplementation

Prophylactic medicinal iron supplementation has been tried in high risk group including infants, preschool and school going children, adolescents, pregnant and lactating women. Such programs take the advantage of reaching masses through these captive high risk targets. Success of such programs will depend on adequate supplies, motivation, network of distribution, side-effects of iron and ultimate compliance of people.

Full term babies should receive 2 mg of elemental iron/ kg/ day starting from 5th month of age onwards and preterm babies 3-4 mg of elemental iron/ kg/ day depending on birth weight starting from 6-8 weeks of age. Preschool children can be reached through Balwadi, Nurseries, Childcare centres and AWW of ICDS projects. School children can be given the iron tablets at school. Pregnant and lactating women can be reached at maternity hospitals, primary health centres and subcentres, family planning centres, immunization centres etc.

Two types of Iron Folic Acid (IFA) tablets are used for this purpose. Adult tablet (greyish white) contains 300 mg of ferrous sulfate (100 mg of elemental iron) and 0.5 mg of folic acid. Pediatric tablet (orange or red colored smaller tablets) contain 60 mg of ferrous sulfate (20 mg of elemental iron) and 0.1 mg of folic acid. Both are sugar coated and are available in a tin containing 1000 tablets. To be meaningful and effective atleast 100 day/ year of supplementation should be given. It is given as 30 tablets per month for 3 months with 10 tablet extra at last month to make it 100 days course. For prophylaxis 1 tablet a day is used and for those with moderate to severe anemia (< 8 g/ dl in children or < 10.0 g/ dl in adults) are given in 1 tablet twice a day for atleast 100 days.

Food Fortification

The most obvious successful example of food fortification is infant milk formula and infant food in West (18). Of course, in our country it is not desirable to use this method as it is costly and can prove hazardous in uneducated and illaffording patients. However, fortification of salt, sugar, rice, fish-sauce etc. can be considered. National Institute of Nutrition, Hyderabad has successfully fortified common edible salt using ferric orthiphosphate and ferrous sulfate with sodium bisulfate. The color or taste do not alter and iron fortified salt has been well accepted. Salt has been selected as it is used daily, by all, irrespective of economic status and there is less margin of overdose as salt cannot be overused. Continuous use of such fortified salt for 12-18 months has shown to lead to a significant drop in the prevalence of iron deficiency in the users. The cost goes up by 15-20 percent due to fortification. Similarly, sugar fortified with iron is also tried and is well accepted and the cost increased only by 2 percent. Government of India has accepted salt fortification in 1985 and tried it in some places.

National Nutritional Anemia Prophylaxis Program (NNAPP)

This program was launched by Government of India in 1970 with an objective of decreasing prevalence and incidence of nutritional anemia in the high risk groups and elimination of nutritional anemia from India by 2000. Stress was laid on targetting high risk groups like infants, preschool and school children, adolescents, pregnant and lactating women and IUD users. They should be reached via primary health centres, subcentres, family planning centers, maternity hospitals, ICDS blocks etc. Focus was put on three areas, first in iron supplementation to decrease the prevalence using iron-folic acid as described before, second to educate people regarding better nutrition and lastly to treat severe anemia to decrease morbidity and mortality related to anemia.

Conclusion

Iron deficiency anemia is still a major health problem of children with adverse effects on the development of the children. It afflicts millions of people, the world over, primarily women of child bearing age, pregnant women and their young children particularly in the developing countries. It is an insidious problem, unnoticed, often not diagnosed, yet it saps the vitality of the nation. Its prevention and treatment requires less share of medical budget. It increases mortality and morbidity in children and pregnant women and reduces physical, mental and intellectual performance, thus reducing the national wealth. Though routine blood tests help in the diagnosis and various tests are available for the confirmation, all those may not be required especially when dealing with masses at large, at the grassroot level who almost invariably require medicinal iron. Cost benefit studies have shown that it makes, economically good sense to prevent this debilitating and sometimes fatal condition by improving the diet by using fortified food. Oral iron therapy is the sheet-anchor of management of IDA. Failure of oral iron treatment is uncommon. Iron supplementation is one of the most cost-effective contributions to the health of children. Anemia control through primary health care should be seen not as an isolated activity but as an integral part of total health care and socio-economic development.

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