Research Paper Management

Management of Iron Deficiency Anemia-Recent Challenges

Dr.R.Perhar

Dr.R.Shukla

Dr.N.Mishra

KEYWORDS

ABSTRACT

Iron deficiency is a common cause of anemia worldwide. Iron deficiency is more than a hematological disorder and affects various other body organs. Lack of screening in large population, concomitant folic acid and B, deficiency, need to distinguish from other causes of microcytic anemia are challenges associated with diagnosis of iron deficiency anemia. Although oral iron is commonest treatment modality used, it is associated with several disadvantages such as need for long term therapy, gastrointestinal adverse effects, and poor patient compliance. Parenteral iron can overcome the shortcomings of oral iron and can replenish iron stores faster and to complete extent as against oral iron. Older parenteral irons such as iron dextran are associated with the risk of anaphylaxis. Choosing the right iron preparation, time constraint in anemia correction especially during pregnancy.lack of public awareness, correction of associated with hookworm infestations are several other challenges in prevention and management of iron deficiency anemia.

Introduction

Anemia is the most common nutritional problem affecting all age groups globally. About 50% of the cases of anemia arc found to be as a result of iron deficiency. Although, iron deficiency anemia (IDA) is most prevalent in pregnant women and young children, it also significantly contributes to morbidity in patients with chronic renal disease, inflammatory bowel disease, heart disease ,hypothyroidism and several other disorders.

The problem of nutritional anemia

Magnitude of problem in INDIA

Prevalence of anemia in India is amongst the highest in the world. India has the highest prevalence of anemia amongst the South Asian countries. Half of the global maternal deaths due to anemia occur in South Asian countries and India contributes to 80% of these deaths. Micronutrient Survey and Micronutrient Survey conducted by National Nutrition Monitoring Bureau (NNMB)] showed that over 70% of the preschool children in India are anemic. Also, NNMB, DLHS and ICMR surveys showed that over 70% of pregnant women and adolescent girls in the country were anaemic. Even amongst higher income educated segments of population about 50% of children, adolescent girls and pregnant women are anaemic.

Factors responsible for high prevalence ofanemia

Nutritional deficiencies of iron followed by folic acid deficiency are major causes of anemia in India. This is due to low dietary intake of iron (less than 20 mg/day), low folate intake (less than 70 meg/day) and poor bioavailability of iron due to high amount of phytates and tannins in the food. The other important contributing factors are chronic blood loss due to hookworm infestation, recurrent malaria or heavy menstrual bleeding, tuberculosis, HIV and deficiency of other important nutrients such as vitamin B12, riboflavin and copper. High prevalence of anemia during pregnancy leads to poor fetal iron stores at birth. Coupled with low breast milk concentration of iron, this is responsible for increased prevalence of anemia in early childhood.

This childhood anemia is aggravated in adolescent girls at the onset of menstruation and early marriages as well as early pregnancy leads to further aggravation of anemia Thus, there is an inter-generational self perpetuating cycle of anemia in Indian population.

Manifestations of Iron Deficiency

Iron deficiency ranges from depletion of tissue iron stores to manifestation of full-blown hypochromic microcytic anemia. The manifestations of iron deficiency are not only limited to reduced oxygen delivery to tissues but also include compromised cell proliferation, metabolism, biotransformation, immune mechanism, cardiac and cerebral function and overall growth. Thus iron deficiency is more than a hematological disorder and affects all body organs.

Often iron deficiency without anemia (depletion of tissue iron stores only) is not treated but has been shown to cause symptoms. In a randomized study conducted in non-anemic women with low ferritin levels who complained of unexplained fatigue, supplementation with oral iron was shown to improve fatigue scale and improve the quality of life

Anemia in obstetrics and gynaecology

Women in pregnancy, during lactation and also during perimenopausal period due to heavy menstrual bleeding are most vulnerable for developing iron deficiency anemia. Anemia during pregnancy is associated with several maternal and fetal complications. Maternal complications include increase fatigability, increased chances of infections, pregnancy-induced hypertension, and postpartum hemorrhage and overall are associated with high maternal mortality. The fetal complications include low birth weight, intrauterine growth retardation, prematurity and increased perinatal morbidity. Treating anemia during pregnancy involves many challenges. Many women are not compliant to the prescribed oral iron therapy as it aggravates the already existing nausea, vomiting and constipation due to pregnancy., Actual bioavailability of the ingested iron is variable due to number of factors including dietary inhibitors, reduced gastric acidity and drug interactions with concomitantly administered medications. Many pregnant women in rural areas present to the antenatal clinic only in late 2nd trimes-

ter or third trimester with moderate to severe anemia. Correction of anemia with oral iron at this stage, decision to go for parenteral iron and assessment of need for blood transfusion are challenges in therapy. Also, active screening and vigilance for anemia in teenage girls and in perimenopausal women is needed in order to identify large number of subclinical cases in the population which do not present to the clinic.

Anemia associated with chronic kidney disease (CKD)

Reduced synthesis of erythropoietin, poor dietary iron intake and chronic systemic inflammation associated with CKD are main factors responsible for anemia in these patients. The consequences of anemia in CKD include increased rate of hospitalization, increased cardiovascular morbidity and mortality, increased transfusion requirements and reduced quality of life. Presence of diabetes, stage 2-3 or stage 5 chronic kidney disease and female sex are associated with increased incidence of anemia in CKD. Due to reduced erythropoietin secretion in the body, CKD patients with iron deficiency most often need ESA (erythroid stimulating agents) therapy coupled with parenteral iron therapy. This is because constant iron availability is required for effective erythropoiesis when the process is stimulated using ESA. However, it is critical to maintain hemoglobin levels between 10-12 gm% in adults with CKD as higher hemoglobin levels may be associated with increased

Table 1: Bioavailability of various iron compounds

Compound	Bioavailability
Ferrous ascorbate	43.7%
Ferrous sulphate	10.4%
Ferric ammonium citrate	2.4%
Ferrous fumarate	8.2%
Sodium iron pyrophosphate	6.3%
Ferric orthophosphate	8.3%

mortality. CKD patients on ESA need critical monitoring of ferritin levels and hemoglobin levels. Ferritin levels > 200 mcg/l, transferrin saturation >20% and percentage of hypochromic RBCs <6% are required to be maintained.

Challenges in the diagnosis of anemia

Iron deficiency anemia or dimorphic anemia due to deficiency of iron and folate is highly prevalent in the community. However, large numbers of cases remain undiagnosed. It is important to confirm iron deficiency using hemoglobin levels, RBC count, MCV (mean corpuscular volume), MCHC (mean corpuscular hemoglobin concentration), MCH (mean corpuscular hemoglobin), ferritin level and transferrin saturation. Concomitant deficiency of vitamin Bl2 also needs to be checked and corrected. Investigations for any ongoing blood loss and malabsorption need to be conducted.

It is important to distinguish between microcytic hypochromic anemia due to iron deficiency and due to other causes like chronic inflammation. High red cell distribution width, low ferritin levels and high total iron binding .capacity (TIBC) with high serum soluble transferrin receptor levels are diagnostic of iron deficiency anemia. On the other hand, high or non-diagnostic ferritin levels, high transferrin saturation levels, low serum soluble transferrin receptor levels can be indicative of anemia of chronic disease or even aplastic anemia. Ferritin levels and transferrin saturation are necessary to be determined in CKD patients. Ferritin being an acute phase reactant the levels are often increased in comparison with non-CKD patients and the diagnostic cut-offs are different for CKD patients.

Challenges in the treatment of anemia

Treatment of anemia mainly consists of use of oral or parenteral iron, correction of vitamin and micronutrient deficiencies including folic acid and vitamin B12 and blood transfusion if needed.

Using oral iron

Oral iron therapy is the most commonly used and cost-effective mode of iron replenishment. However, absorption of oral iron and compliance to oral iron therapy remain the most important challenges with oral iron therapy.

Absorption of oral iron

Absorption of oral iron is dependent on several factors. Iron in the form of ferrous ions is easily absorbed as compared to ferric ions. Absorption of ferric ion is dependent on enzyme ferric reductase present on the brush border of the duodenum. Ferric reductase activity is dependent on vitamin C deficiency which prevents conversion of ferric to ferrous ions thus limiting absorption, Presence of dietary inhibitors mainly phytates and tannins inhibit absorption of iron from intestines. Concomitant intake of calcium based antacids and proton pump inhibitors reduce absorption of oral iron. Disruption of gastrointestinal mucosa due to ulcerative colitis or Crohn's disease can hinder iron absorption.

Also, absorption of different oral iron compounds is different giving rise to variable therapeutic response

Tolerability of oral iron and compliance

Oral iron preparations are commonly associated with side effects such as metallic taste, nausea, constipation or diarrhea and black discoloration of stools. Due to variable iron absorption, oral therapy requires long periods of treatment. In case of troublesome adverse effects, patients may not be compliant for the duration of therapy. Inadequate treatment with oral iron may correct hemoglobin levels to some extent but iron stores remain uncorrected.

Table 2 shows advantages and disadvantages of using oral iron therapy.

Using parenteral iron

Choice of parenteral iron, safety of parenteral iron and affordability are major challenges in using parenteral iron.

Table 2: Advantages and disadvantages of oral iron

Advantages	Disadvantages
• Easy availability • Affordable • Can be self-administered • No risk of serious adverse reactions • Low risk of hypersensitivity	• Require patient adherence to treatment • Long treatment periods required • Does not ensure complete bioavailability of iron • Common GI adverse effects impair patient compliance • Does not replenish iron stores

- **Choice of parenteral iron**

Older iron preparations such as iron dextran are easily affordable but require administration of test dose. Even then anaphylaxis is not ruled out.

Iron sucrose is a safe option that does not need test dose but cannot be used at doses higher than 200 mg thrice weekly (except nephrology patients where 300-400 mg have been used). Ferric carboxymaltose shares the beneficial properties of iron dextran and iron sucrose and is an important therapeutic advance in the treatment of iron deficiency anemia. Ferric carboxymaltose is a robust and stable iron (III) hydroxide- carbohydrate complex like iron dextran which can be infused as up to 1000 mg in a single-intravenous infusion over a period of 15 minutes safely. It lacks hypersensitivity associated with iron dextran and does not require adminis-

tration of a test dose. Although iron sucrose also lacks the hypersensitivity, it has to be given in the form of small i.v. infusions to avoid the release of free iron that can result into acute toxicity as mentioned earlier. To provide a dose of 1000 mg, iron sucrose needs to be given in the form of 5 doses of200 mg each over 14 days period. As against this, total iron replenishment can be achieved with one or two infusions of FCM. Thus, total dose infusion with FCM can reduce the number of patient visits and venepunctures and is a more convenient form of parenteral iron therapy. Table 3 gives comparison of parenteral iron compounds.

However, for correction of anemia during pregnancy, iron sucrose is a safer option with more clinical experience in its usage and is recommended by guidelines.
UK guidelines [2012] by British Society for Haematology. Obstetric Haematology Group (BSH OHG) and British Committee for Standards in Haematology (BCSH) recommend that although oral iron therapy should be given as a first line of therapy, parenteral iron should be considered from the second trimester onwards and during the postpartum period for women with confirmed iron deficiency who fail to respond to or are intolerant of oral iron. Parenteral iron therapy is recommended by Royal College of Obstetricians and Gynecologists guidelines [2013] when there is absolute non-compliance with, or intolerance to, oral iron therapy or proven malabsorption.

Table 3: Comparison of parenteral iron preparations

Parenteral iron Preparations	Stability of complex (type)	pH	Osmolality	Antigenicity	Time required for administration	Maximum dose (mg of iron)	Reduction potential (mV)
Ideal	High	Neutral	Isotonic	Low	Short	High	<-324
Iron dextran	High (I)	Neutral	Isotonic	High	1.5h for 7 mg Fe/kg b.w.	500 mg/week	-526
Iron Sucrose	Moderate (II)	High	High	Low	6 h for 20 mg Fe/kg b.w.	20 mg Fe/kg b.w.	-475
Ferric carboxy-maltose	High (I)	Neutral	Isotonic	Low	15 min for 15 mg Fe/kg b.w.	1000 mg/week	-390

Safety of parenteral iron
Iron dextran can give rise to life threatening anaphylactic reactions. Although test dose is not recommended for iron sucrose injection, it is needed to strictly monitor the patient during and after infusion. Administration of higher doses, higher dilutions or prolonged infusions may result into free iron reactions in the form of hypotension, gastrointestinal disturbances, shivering etc. Ferric carboxymaltose does not require test dose and can be administered at doses up to 1000 mg/ infusion/ week

Important Issues In Management Of Iron Deficiency Anemia

Time constraint in the management of anemia

Moderate to severe anemia correction requires prolonged therapy with oral iron. In such cases, IV iron is preferred as it corrects the total iron deficit immediately and is associated with faster hemoglobin rise than oral iron. In preoperative anemia correction or correction of anemia in the third trimester require early rise of hemoglobin levels that may need blood transfusion. It is a critical to decide between IV iron and blood transfusion. Timely use of IV iron can avoid the risk of transmission of serious infections associated with blood transfusion.

Replenishment of iron stores
Even if compliance can be overcome, replenishment of iron stores is a challenge. The calculated cumulative deficit plus quantity for stores must be administered. This is conveniently possible in fewer sessions with ferric carboxymaltose than iron sucrose. Even when oral iron increases hemoglobin, it seldom builds up the ferritin stores. IV iron is particularly successful in increasing ferritin levels quickly.

Blunted erythropoiesis
Reduced erythropoietin response disproportionate to the degree of anemia is seen in certain medical conditions including early pregnancy. In the first half of pregnancy, the plasma levels of EPO are relatively low which give rise to blunted erythropoiesis. This is recovered late in the pregnancy. The reason is probably increase in the systemic markers of inflammation. This usually does not require treatment with rHuEPO and is corrected in the third trimester.

Similarly, many patients with congestive heart disease or post-trauma patients show anemia of chronic diseases with blunted erythropoietic response. This is probably due to the complex interactions between low hemoglobin levels, hypoferric state and increased inflammatory markers. Such cases may need intravenous iron therapy along with subcutaneous ESA

Challenges in the prevention of anemia

Prevention of anemia at community level can be achieved by number of ways such as increasing public awareness about anemia and its consequences, inculcation of good dietary practices in order to maximize iron absorption, fortification of certain food items with iron, active screening for anemia in high risk groups - children, elderly, women in reproductive age group, regular deworming for prevention of worm especially hookworm infestation and spacing of pregnancies which allows iron stores to replenish.

Conclusion

Nutritional anemia mainly arising due to iron deficiency is prevalent in Indian population. In spite of number of oral and parenteral iron preparations available, control of causative factors, improving patient compliance, choosing the right oral or IV iron still remain challenges in clinical practice.

REFERENCES

1. [Guideline] Qaseem A, Humphrey LL, Fitterman N, et al. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. Dec 3 2013;159(11):770-9. | 2. Brooks M. Iron Deficiency Linked to Psychiatric Disorders in Kids. Medscape Medical News. Available athttp://www.medscape.com/viewarticle/806778. | 3. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study.BMC Psychiatry. Jun 4 2013;13:161. | 4. Mateos Gonzalez ME, de la Cruz Bertolo J, Lopez Laso E, Valdes Sanchez MD, Nogales Espert A. [Review of haematology and biochemistry parameters to identify iron deficiency] [Spanish]. AnPediatr (Barc). Aug 2009;71(2):95-102. | 5. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. Oct 2011;60(10):1309-16. | 6. DeLoughery TG. Microcytic anemia. N Engl J Med. Oct 2 2014;371(14):1324-31 | 7. Koutroubakis IE, Oustamanolakis P, Karakoidas C, Mantzaris GJ, Kouroumalis EA. Safety and efficacy of total-dose infusion of low molecular weight iron dextran for iron deficiency anemia in patients with inflammatory bowel disease. Dig Dis Sci. Aug 2010;55(8):2327-31. | 8. Onken JE, Bregman DB, Harrington RA, Morris D, Buerkert J, Hamerski D, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. Nephrol Dial Transplant. Aug 20 2013; | 9. Brooks M. FDA Approves Injectafer for Iron Deficiency Anemia. Medscape Medical News. Available athttp://www.medscape.com/viewarticle/808800. Accessed August 3, 2013. | 10. Grogan K. Vifor gets FDA approval for Injectafer. PharmaTimes. Available athttp://www.pharmatimes.com/Article/13-07-26/Vifor_gets_FDA_approval_for_Injectafer.aspx. | 11. Fernandez-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. Cochrane Database Syst Rev. Dec 7 2011;12:CD009218. | 12. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database Syst Rev. Dec 7 2011;12:CD009085. |