Management of Iron Deficiency Anemia - A Tale of 50 Years

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With the 1967 January issue, *Indian Pediatrics* embarked upon a new journey under the stewardship of a new editor, Dr NG Mojumdar. This issue consisted of 64 pages, with five research papers (phenylalanine metabolism in protein calorie malnutrition, relationship of skeletal maturation with nutrition, two studies on parenteral iron, and rectal bleeding in childhood) as well as other regular features. As iron deficiency is one of the most common micronutrient deficiencies encountered by pediatricians, we discuss how the management of iron deficiency anemia (IDA) has evolved in the last fifty years.

THE PAST

The study [1] entitled 'Single dose intravenous iron infusion in treatment of iron deficiency anemia' was conducted by at the Central Railway Hospital in Bombay. In those days, a few studies in adults from Western countries had demonstrated superior results of single intravenous iron infusions compared to the standard practice of giving multiple injections when oral preparations were ineffective. The authors had observed that their patients who resided outside Bombay were less compliant with iron therapy, and were irregular in follow-up. Thus, they felt that a single dose would be a suitable alternative therapeutic option. Over a period of six months, children with IDA and hemoglobin (Hb) < 7 g/dL were enrolled; initially in-patient and subsequently out-patient. The final study population comprised of 70 children (50% under the age of three years with equal gender ratio). Baseline hematological investigations were performed to establish IDA. Following a test dose, a single intravenous infusion of Iron-Dextran complex was administered (dose according to a standard formula based on body weight and hemoglobin deficit). Patients were monitored for 4 hours for adverse reactions and asked to return at 6 weeks. The outcome variable was the percentage of children demonstrating a significant (≥3 g/dL) increment of Hb. Low- to moderate-grade fever was observed in 71.4%, allergic reactions (urticarial rash, itching, flushing and facial puffiness) that responded to anti-histaminic drugs in 10%, local reactions (soreness at infusion site) in 28.5%, and thrombophlebitis in 2.8% children. Once safety was established, enrolment of out-patients began. A successful response ranging from 50% to 76.6% (stratified according to baseline Hb levels) was observed in the children who followed-up at 6 weeks (42.9%), and from 85.7% to 100% in the remaining who followed-up at 12 weeks. A better response was noted in children who had a lower pre-infusion Hb level in both groups. Authors concluded that a single intravenous dose of iron-dextran countered the challenge of non-compliance, showed faster hematological response, was less time consuming and economical, and could be used safely in outpatient settings for treatment of IDA.

Historical background and past knowledge: Iron salts have been used therapeutically since more than 300 years. Earlier use was based on the symbolic trans-cultural belief that iron was associated with strength. The medicinal use of iron for treating 'chlorosis' (described as a condition characterized by a greenish-yellow discoloration of the skin) by Syndenham in 1681 has been reported in the literature [2]. In 1713, Lemery and Geoffy inferred that iron was a constituent of blood by demonstrating its presence in the ash of burnt blood [3]. Pierre Blaud revolutionalized iron therapy in the early nineteenth century by developing iron pills (combinations of ferrous sulfate and potassium carbonate) for ingestion [4]. Subsequently, many other oral formulations emerged, but all of them had a common drawback of being less efficacious in malabsorptive disorders, and were dependent on compliance. The first

parenteral preparation, Ferric hydroxide, introduced in the early 20th century, was administered by both subcutaneous and intramuscular routes, but was discontinued due to severe toxic reactions. Subsequently, a supposedly safer intravenous preparation – saccharated oxide of iron – was developed by Nissim in 1947, but subsequently was found to have serious adverse effects. The preparation used in this study Iron-Dextran complex (Imferon) was developed by Baird and Podmore in 1954. This had a surrounding carbohydrate shell which controlled the release of free iron. Later it also fell into disrepute due to anaphylactic reactions. The study by Kango and Varudkar [1] also reported hypersensitivity reactions in 10% of children.

THE PRESENT

Iron deficiency anemia remains one of the most common causes of nutritional anemia globally, especially in low- and middle-income nations. In India, the prevalence of nutritional anemia remains high and largely unchanged over the last few decades despite the implementation of many community-based strategies. The third National Family Health Survey (NFHS) in 2005-06 reported 80% children under 2 years and 70% under 5 years as anemic, and NHFS-4 (2014-15) reported variable prevalence of anemia in various states ranging from 23% (Manipur) to more than 70% (Bihar) in children between 6 to 59 months [5,6].

As the first line of treatment, oral iron is relatively inexpensive, safe and efficacious. Till around a decade ago, the oral dose of iron therapy in children was 4-6 mg/kg/day of elemental iron [7]. The discovery that the duodenal absorptive capacity was saturated by 25 mg was the basis for reducing the dose to 3 mg/kg /day [8]. Currently there are many iron salt preparations (sulfate, fumarate, succinate, gluconate, glutamate, lactate, ammonium citrate, amino-acid chelates, polymaltose Complex, carbonyl, colloidal, and heme-based) overwhelming the market, which makes it difficult for the pediatricians to decide what to prescribe [9]. Adverse effects are gastrointestinal side-effects (that can be minimized by administering in divided doses between meals), staining of teeth (reduced by rinsing of mouth) and an astringent taste (that varies among compounds). These side effects and long duration of therapy often lead to non-compliance.

Indications for intravenous iron include conditions that render oral iron therapy ineffective (ongoing blood loss, worm infestation, malabsorptive syndromes and gastrointestinal cancer) and the functional iron deficiency that arises from the increasing use of erythropoiesis-simulating agents in patients with chronic kidney disease. Currently used parenteral preparations are low molecular weight (LMW) iron-dextran, iron sucrose and ferric gluconate. Recently, third generation formulations (like ferumoxytol, ferric carboxymaltose and iron isomaltoside 1000) have emerged, which are iron-carbohydrate complexes that slow the release of iron resulting in more favorable safety profiles.

Various programs have been initiated by the Government of India with the common goal of clinically screening the high-risk populations, and either providing prophylactic or therapeutic supplemental iron. More recently, the National Iron Plus Initiative [10] provides weekly/bi-weekly age-stratified iron and folic acid supplementation to children, adolescents and women, irrespective of their iron or hemoglobin status. With constant efforts from the government and increasing sensitization of the community to the clinical implications of iron deficiency, importance of prophylactic iron and optimum nutrition; we will hopefully be able to see a uniform decline in the prevalence of IDA nationwide by the time the next NFHS is conducted.

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