



## Parenteral iron therapy in children with iron deficiency anemia

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### Abstract

Iron deficiency anemia (IDA) continues to be a global public health problem. Oral iron is the universally accepted first-line therapy, and most children have a prompt and favorable response to oral formulations. In subsets of children who fail to respond due to intolerance, poor adherence, or inadequate intestinal absorption, parenteral iron is indicated. Despite numerous studies in adults with IDA of diverse etiologies, pediatric studies on parenteral iron use are very limited. Although mostly retrospective and small, these studies have documented the efficacy and safety profile of intravenous iron formulations. In this editorial the author comments on the most important published data and underscores the need to seriously consider parenteral iron use in children unresponsive to oral therapy.

**Key Words:** Anemia; Iron deficiency; Intravenous iron; Iron deficiency anemia; Children

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**Core Tip:** Intravenous iron is an important but underutilized therapy in children with iron deficiency anemia (IDA) who fail to respond to oral iron. Considering IDA-related long-term negative neurobehavioral effects, it is important to switch to intravenous iron timely and safely. Over the last decades there has been a remarkable improvement in the quality of intravenous iron formulations with greater efficacy, tolerability, and safety.

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## INTRODUCTION

Iron deficiency anemia (IDA) is a global public health problem, particularly affecting young children and women of childbearing age in low-income countries[1]. Despite worldwide prevention and control strategies, IDA is still common in developed countries, with an estimated prevalence of 20.1% in children under the age of 4 years[2]. Common risk factors for IDA in early childhood include poor dietary intake, prematurity, rapid growth, and gastrointestinal blood loss due to excessive consumption of cow's milk. The clinical presentation varies, ranging from asymptomatic to excessive irritability or lethargy, tachypnea, and heart failure. Symptoms and clinical signs depend on the age of the affected child, the underlying condition, the rate of onset, the duration and the severity of anemia, and comorbidities[3,4].

Regardless of the presence of symptoms, children with iron deficiency and IDA should receive timely treatment, because they are at risk for long-lasting neurocognitive impairments, altered motor functions, decreased school performance, and behavioral disorders[4]. The mainstay of the treatment includes iron supplementation, together with the investigation and correction of the underlying cause of IDA. Peroral iron substitution is the universally accepted first line therapy of IDA or iron deficiency without anemia. The excellent efficacy, safety and cost profile of oral formulations are well documented, but guidelines vary[5-7]. Oral iron should generally be taken at least 1 to 2 h before or after meals, to ensure better absorption. Children sometimes dislike oral iron preparations due to their metallic taste. Gastrointestinal side effects, such as abdominal pain, nausea, vomiting, diarrhea, or constipation, have been reported in up to 32% of patients and can lead to low compliance or discontinuation of therapy. To limit side effects and ameliorate adherence to treatment, some current therapeutic regimens favor lower dosages and less frequent administration (alternate-day dosing) of oral iron[5]. Other strategies include formulations with higher bioavailability and fewer adverse gastrointestinal effects, such as bis-glycinate chelate iron and liposomal iron[5,8]. Detailed education of the family about possible side effects is recommended from the beginning of treatment to improve adherence.

Despite these efforts, there is a small proportion of children who do not tolerate or are refractory to oral iron administration. Moreover, oral iron therapy frequently fails in children who present with gastrointestinal tract disorders, such as intestinal failure, inflammatory bowel disease, coeliac disease, *Helicobacter pylori* infection, chronic gastrointestinal bleeding, or tropical parasitosis[9,10]. Besides, pediatric patients may have iron absorption defects due to prolonged use of medications, such as proton pump inhibitors and histamine-2 receptor antagonists[11]. Finally, oral iron therapy is inadequate when a rapid increase in iron levels is required to avoid blood transfusion, such as severe perioperative IDA related to surgery with high blood loss[12].

In all the above pediatric conditions, parenteral iron therapy should be considered. However, the available pediatric experience with intravenous iron products as an alternative to oral iron is very limited outside the context of chronic kidney disease, where the patient is mainly hemodialysis-dependent and receiving recombinant erythropoiesis-stimulating agents[13-15]. There is a widespread belief among pediatricians that parenteral iron is avoided in children with IDA unless severe malabsorption or a serious condition is present. Major concerns about adverse reactions such as life-threatening hypersensitivity further contribute to the avoidance of parenteral iron therapy in pediatric practice[16].

Due to the wide range of underlying IDA-associated etiologies that could benefit from parenteral iron administration, some small but noteworthy pediatric studies have documented the safety and efficacy of parenteral iron. As intramuscular iron injections have long been avoided due to local pain, skin pigmentation, and the potential risk for rhabdomyolysis and sarcoma arising at the injection site, intravenous iron formulations are the only alternative to oral administration[17].

The first-generation intravenous iron products in the form of high molecular weight iron dextran were associated with unfavorable safety profiles, and have been abandoned in pediatric use[18]. Pinski *et al*[19] first reported the second-generation intravenous iron product - iron sucrose - as an effective and safe means in 45 children with IDA who did not respond to oral iron therapy. They observed a statistically significant rise in hemoglobin concentrations 14 d after the first iron dose and 6 months following completion of therapy, and only one severe side effect with transient hypotension. Similar results with second-generation formulations were consecutively confirmed in several studies that included limited numbers of children with IDA, from 11 to 38[20-23]. The largest study was conducted by Kaneva *et al*[24], who reported a moderate increase in hemoglobin and a substantial improvement in iron after administration of intravenous iron sucrose in 142 patients with IDA (aged 7 months to 22 years), not compliant with oral formulations or with malabsorption. Broader experience across various specialties (excluding nephrology) incorporated 194 patients who received a total of 1088 intravenous iron doses. No severe infusion-associated reactions occurred. Although lacking standardization in the indications, formulations, or dosing, the data supported previous findings that intravenous iron should be considered as an efficacious and extremely safe alternative for IDA treatment in children in whom oral iron had been either unsuccessful or was contraindicated[25].

The next challenge was to address the issue of reducing the need for repeated intravenous infusions and administering larger amounts of iron in a shorter period. The third-generation intravenous iron product ferric carboxymaltose was approved for pediatric patients over the age of 14, having the advantage of being administered not only as a single shot and without a test dose, but in a lower dosage and with a shorter infusion time than second-generation preparations[5, 10]. Several reports have provided evidence for the excellent efficacy and safety profile of intravenous ferric carboxymaltose in children and adolescents with IDA of diverse etiologies[26-30].

The main benefits of intravenous iron compared to oral iron administration are the reduction in non-adherence related to gastrointestinal side effects, and the bypassing of the intestinal absorption, thereby avoiding further mucosal damage. In addition, parenteral iron is indicated in cases of intolerance or refractoriness to oral formulations in children with severe IDA with ongoing bleeding, where the iron loss is greater than oral iron can supply, and in children with chronic kidney diseases who are on hemodialysis. Nevertheless, current practice provides evidence of the underuse of parenteral iron in children. Safety concerns frequently cause physicians and parents to be reluctant to switch to intravenous iron.

Although adverse reactions are rare with careful patient monitoring in a hospital setting with experienced staff, the potential disadvantages of parenteral iron include lower availability, higher cost, and the greater impact on the child due to venipunctures and the clinical environment. Furthermore, the risk of iron overload, burdened by a potential proinflammatory effect, should always be considered.

There are insufficient data on the pharmacokinetics and pharmacodynamics of different iron preparations in the pediatric population. Repeated administration of iron sucrose, the most frequently used intravenous iron preparation in children, was effective in raising hemoglobin concentrations to normal in all children with IDA within 31-42 d after the first infusion[22]. Administration of a single dose of intravenous ferric carboxymaltose in children unresponsive to oral iron therapy showed a complete hematological response in 49% of patients with IDA and 85% of all patients reached the target ferritin level within 12 wk post-treatment[30]. Likewise, dose-related increases in ferritin and transferrin saturation and clinically meaningful increases in mean hemoglobin concentration were observed from baseline to 35 d after a single intravenous dose of ferric carboxymaltose in children with IDA[31]. These pharmacokinetic studies provide useful information regarding the optimal dosing regimen and potential adverse events, but more detailed investigation is required to better understand and predict the bioavailability of iron preparations[32].

Oral iron therapy with standard ferric salts is by far the lowest cost option and is readily available, but often of limited efficacy, with frequent gastrointestinal side effects and poor adherence. Conversely, intravenous iron formulations are associated with significant cost, yet have been previously shown to replenish hemoglobin levels more effectively than oral iron[33,34]. Older-generation intravenous iron products have lower prices than newer-generation products. However, the latter may be associated with a reduction in total cost of care, mainly due to the lower number of venipunctures, better adherence, lower cumulative chance of infusion reactions or extravasations, and increased convenience for physicians and patients[35]. For all these reasons, physicians should consider the underlying disorder, the therapy goal, the response to prior therapy, patient tolerance and adherence, the cost, and the ease of access to the treating center when deciding on which formulation to use.

High oral iron doses or rapid iron release from intravenous formulations can saturate the iron transport system, resulting in oxidative stress, with adverse clinical and subclinical consequences[32]. A common concern is that intravenous iron may promote or exacerbate inflammation in anemic patients by triggering macrophage activation. While some studies have shown a transient increase in the circulating inflammatory cytokines interleukin (IL)-6, tumor necrosis factor- $\alpha$ , chemokine ligand 2 and interferon gamma[36], others observed no effect on the inflammatory markers IL-6 and IL-10[37]. Further research is required to better understand the pro-oxidant and proinflammatory potential of intravenous iron.

Altogether, clinical studies have clearly demonstrated that the benefits of parenteral iron strongly outweigh any potential harm. With the growing evidence supporting a wider range of indications for parenteral iron in children, and with the availability of new iron formulations, randomized prospective trials are needed to establish practical recommendations for the most appropriate strategies in pediatric practice.

## CONCLUSION

Intravenous iron has become a major therapeutic modality for IDA in pediatrics when oral iron preparations are unsuccessful. Proper utilization of intravenous iron offers significant clinical benefits by reducing morbidity from many IDA-related pathological conditions in children.

## FOOTNOTES

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