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PARENTERAL IRON THERAPY IN CHILDREN WITH IRON DEFICIENCY ANEMIA

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Objective – The aim of the study was to determine the efficacy and safety of intravenous iron preparations in a group of children with iron deficiency anemia who did not respond to oral iron supplementation. **Materials and methods** – We conducted a retrospective study on children who received intravenous iron sucrose and iron gluconate at University Children's Hospital Rijeka between January 1, 2010 and December 31, 2011. The response to therapy was determined by the difference in the hemoglobin values prior to parenteral treatment and after two months. **Results –** A total of 76 intravenous iron infusions were administered to twelve children. Patients had a good response to parenteral iron therapy, with a median hemoglobin rise of 2.7 g/dl within two months. There was only one mild adverse reaction. **Conclusion –** Parenteral iron therapy should be considered in a group of children with iron deficiency anemia who fail to respond to oral iron preparations due to malabsorption, intolerance or poor compliance. The possible occurrence of severe adverse reactions emphasizes the need for close medical observation.

Key words: Intravenous iron ▪ Anemia ▪ Iron deficiency ▪ Child.

Introduction

Iron deficiency anemia (IDA) continues to represent a major public health problem, particularly in infants and young children. It is estimated that 40% to 50% of children under 5 years of age in developing countries are iron deficient (1). A common etiology of IDA is poor dietary iron intake, especially excessive consumption of cow's milk. Other causes of IDA in children are increased iron requirements during the growth period, inadequate absorption or utilization of iron, and blood loss (2). The treatment consists of iron supplementation along with improved nutrition. In vast majority of iron-deficient anemic children, oral administration of simple ferrous salts provides effective and inexpensive therapy (3). Parenteral iron preparations are infrequently indicated, mainly for children with malabsorption or poor compliance. Besides, some adverse reactions reported with intravenous iron administration have led to its limited use in children (4). We conducted a retrospective study in which intravenous infusions of iron sucrose and iron gluconate where administered to pediatric patients with IDA who failed to respond to oral iron supplementation.

The goal of the study was to determine the efficacy and safety of intravenous iron preparations.

Patients and methods

Medical records were reviewed on all patients who received intravenous iron preparations at the Division of Hematology and Oncology, University Children's Hospital Rijeka, between January 1, 2010 and December 31, 2011. Data abstracted included age, gender, medical history leading to iron deficiency, underlying disease, prior oral iron supplementation, indication for parenteral iron, laboratory values before and after parenteral therapy, and adverse reactions. Stool was examined for the presence of blood and parasites. All tests were done at the same laboratory. The Institution Review Board approved this retrospective study. The response to intravenous iron was determined by the difference in the hemoglobin concentration values prior to parenteral treatment and two months after the start of the treatment. Student t-test was performed with significance set at 0.05.

Results

Twelve patients received intravenous iron during the study period. Children ranged in age from 13 months to 14 years (median 5.8 years). Male to female ratio was 1 to 1. Before intravenous iron therapy, seven children underwent iron absorption test (10 mg/kg elemental iron, measuring serum iron immediately before and 2 hours later) (6), which showed no increase in serum iron. In anemic children who were non-adherent to oral iron therapy, iron absorption test was not performed. Patients, basic conditions leading to iron deficiency, indications for parenteral iron, total dosage and number of intravenous infusions are summarized in Table 1.

Seven children, aged 1 to 3 years, had poor iron dietary intake. Two of them were twin boys who were born premature (birth weight 1700 g and 1800 g), fed with iron-fortified formula, not started mixed food, and received no supplemental medical iron until the age of 11 months. Three adolescent girls had menorrhagia. One teenage girl had anemia due to insufficient iron intake and chronic gastritis. She was frequently taking antacids that contain calcium, thus decreasing absorption of iron from foods. One boy had documented cow's milk allergy and chronic blood loss detected with chemical testing of stool specimens.

All patients were treated with oral iron (length of treatment varied by patient's weight and compliance) before using parenteral delivery. Six patients had poor response to oral iron supplementation. Five children had low com-

Table 1 Characteristics of 12 patients receiving intravenous iron

Patient	Sex	Age (years)	Etiology of iron deficiency	Indication for parenteral iron	Total dose of iron (mg)	Number of doses
1	F	13	Menorrhagia	Non-adherence to oral iron	1800	9
2	F	14	Menorrhagia	Intolerance to oral iron	1400	7
3	F	14	Menorrhagia	Intolerance to oral iron	1400	7
4	F	14	Chronic gastritis, Poor dietary intake	No response to oral iron	2000	10
5	M	2	Cow's milk allergy / Chronic blood loss	Non-adherence to oral iron	125	2
6	M	2	Poor dietary intake	No response to oral iron	375	6
7	M	2	Poor dietary intake	Non-adherence to oral iron	375	6
8	F	3	Poor dietary intake	Non-adherence to oral iron	375	6
9	M	1	Poor dietary intake, Premature twin	No response to oral iron	375	6
10	M	1	Poor dietary intake, Premature twin	No response to oral iron	375	6
11	F	2	Poor dietary intake	No response to oral iron	250	4
12	M	2	Poor dietary intake	Non-adherence to oral iron	437.5	7

pliance; in three of these cases, there was low compliance by parents. Two adolescent girls claimed side effects as the main obstacles for inadequate iron supplementation. Only one patient had low toleration of the oral formulation.

Iron was administered intravenously as iron sucrose (Venofer) and iron gluconate (Ferrlecit). Venofer is supplied in ampules of 5 ml containing 100 mg of elemental iron. Each vial of 5 ml of Ferrlecit contains 62.5 mg of elemental iron. The total amount of required iron was calculated according to the body weight and amount of desired change in hemoglobin using the following formula (5): Total dose of iron (mg) = [Target hemoglobin – actual hemoglobin] (g/dl) x weight (kg) x 0,24 + [15 x weight (kg)]. Total cumulative dose was divided and given every 3 to 7 days (average time 6.3 days), until desired dose is achieved. Daily dosage was 5 to 7 mg of elemental iron per kilogram. Maximum single dose was 200 mg. Before administering the first dose to each patient, a test dose was administered. For children weighting <10 kg, the test dose was 10 mg; for children weighting 10 to 20 kg, the test dose was 15 mg; for other pediatric patients, the test dose was 20 mg. The test dose was diluted in 50 ml of 0.9% sodium chloride and administered over 60 minutes. If no adverse reactions were seen during infusion and after 30 minutes, the remaining dose was administered. Subsequent routine doses were given without a test dose. The iron preparation was diluted up to 0.8 mg of elemental iron in 1 ml of normal saline solution and infused over 1 to 2 hours, depending on dose and patient weight. Maximum dilution was 250 ml of normal saline.

Four patients received iron glucose and eight patients received iron gluconate. A total number of 76 doses was administered. The number of intravenous iron infusions per patient ranged from 2 to 10 (median 6.3), and the individual doses were 62.5 and 200 mg (median 108.3 mg). Twelve of the total 76 doses were preceded by a test dose.

Mean hemoglobin level before treatment was 8.7 g/dl (SD=1.7), ranging from 6.5 to 10.6 g/dl. After two months mean hemoglobin value was 11.7 g/dl (SD=1.0), ranging from 11.0 to 13.2 g/dl. Intravenous iron led to a significant increase ($p<0.005$) in hemoglobin concentration of 2.7 g/dl within 2 months (range 0.4 to 5.4 g/dl). Fig. 1 shows the response to intravenous iron preparations.

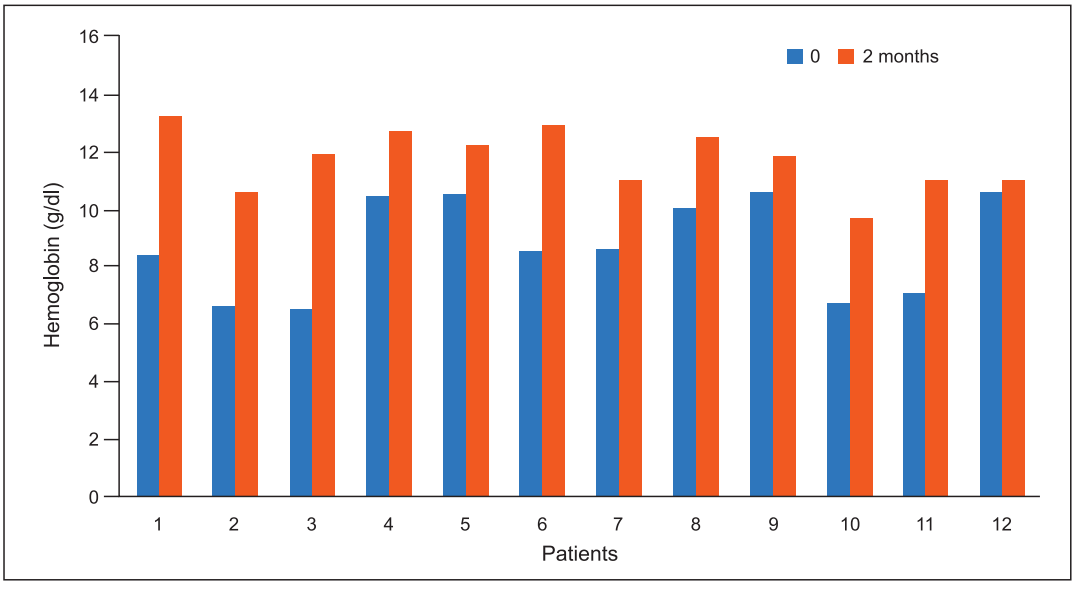

Fig. 1 *Hemoglobin levels before and 2 months after the beginning of intravenous iron therapy.*

Among 12 children who received a total of 76 doses of iron sucrose and gluconate, 1 mild adverse reaction was attributed to the infusion. The patient experienced headache and transient mild hypotension one hour after the initiation of third intravenous iron sucrose, and the infusion was discontinued. Following intravenous iron administrations were uneventful. One patient had drug extravasation, with pain and discoloration at the site of injection, which resolved within 2 days. No other adverse reactions were reported by patients or their parents.

Discussion

IDA is the most common cause of anemia worldwide, particularly in children and women of childbearing age. In infants and young children, consumption of foods with low bioavailable iron is likely the primary contributing factor. Rapid growth may outpace dietary intake of iron, and result in iron deficiency without disease or apparently abnormal diet (7). Preterm and low-birth-weight infants are at greater risk for IDA. Other risks include inadequate iron absorption, chronic blood loss, and some other medical conditions that affect iron status (1).

In the present study the main condition leading to IDA was poor dietary intake, mostly in young children. This finding points the importance of various dietary interventions in the prevention of IDA, including breastfeeding, fortification of formula if not breast-fed, and in time introduction of iron-containing complementary foods (8, 9). Adolescent girls are at risk for IDA because of several factors, including menstrual bleeding, growth spurts, and fad dieting that restricts eating. Majority adolescents in this study had IDA due to heavy menstrual blood loss. Measures to alleviate menstrual disorders should be a part of the strategy to reduce IDA.

The goal of the therapy is both replenishment of body iron stores and correction of anemia. In vast majority of cases, oral iron supplementation is effective, fast and inexpensive therapy. Infrequently, the response to oral iron preparations is unsatisfactory, mostly when malabsorption is present or when compliance is poor. In such cases parenteral iron is needed (10, 11).

Parenteral iron has been administered intramuscularly or intravenously. As intramuscular injections are painful, and have been linked with gluteal sarcoma, it is recommended that the use of intramuscular iron should be abandoned (12, 13). Several formulations of intravenous iron have been approved worldwide, including iron, sucrose, dextran, sucrose, gluconate, carboxymaltose, isomaltoside, and ferumoxytol (14, 15). The largest experience in published literature is with iron sucrose and iron gluconate, which we used in this study. Intravenous iron can be given in a variety of schedules. The frequency of therapy can be thrice weekly, twice weekly, weekly, or every other week, depending on the indication, pretreatment hematological values, target hemoglobin, response to therapy, treating physician opinion, and center experience. The total amount of parenteral iron required to raise hemoglobin to normal levels and replenish iron stores is calculated according various formulas, and dosing calculators are widely accessible. Dosing to children should be adjusted to weight (1, 15).

There are very few studies on parenteral iron administration in pediatric practice for non-renal indication. Pinsk and coworkers reported an excellent response to intravenous iron sucrose in 45 children who failed previous treatment with oral iron (16). The best described series includes 38 children who received iron sucrose; 13 with no response to previous oral iron, 13 with iron malabsorption or dependence on parenteral nutrition, 7 with gastrointestinal blood loss, and 5 with other indications (17). Patients in all categories had a good response to intravenous iron.

In our study, the most common reason to parenteral iron treatment was lack of the response to oral iron. In this patient group, we performed oral iron absorption test, which confirmed disturbed intestinal iron absorption. Although failure to absorb iron is mostly due to an underlying malabsorption syndrome, prolonged IDA itself may impair intestinal absorption of iron in some children, thus necessitating parenteral iron for correction (6). Other indications for parenteral therapy in the present study included nonadherence to oral therapy and intolerance to oral iron. Intolerance was not observed in young children, but in two adolescents who had gastrointestinal complaints.

Eleven patients out of twelve showed improvement in hemoglobin levels at the end of the treatment. The only patient who had no significant increase in hemoglobin concentration was a 2-year-old boy with allergy to cow's milk protein (no 5). The child had started with milk free diet including soy-based formula that he tolerated well. His parents were not adherent to a prescribed course of oral iron, and refused parenteral iron after two doses.

Severe systemic reactions after parenteral iron administration have been reported in the literature, with possible fatal outcome. Iron dextran has higher incidence of anaphylaxis compared to iron sucrose and iron gluconate (18). Use of these preparations may rarely be associated with hypotension, flushing, abdominal pain, and nausea/vomiting. Prior to initiating intravenous iron therapy, a one-time test dose has traditionally been given, but a limited value was noted. A test dose neither minimizes reactions to the first dose, nor prospectively identifies the patient at increased risk for a severe reaction to a later doses. Therefore, caution is warranted with every dose of intravenous iron formulation that is administered (19). Our group of patients tolerated parenteral iron very well, except one patient (no 3) who experienced a mild systemic reaction during the administration of the third dose. Although the number of patients included in this study is small, our preliminary results suggest that parenteral iron therapy could be a safe and efficacious means to treat IDA in children who do not tolerate oral iron therapy for any reason. Reporting of adverse events to central agency should be mandatory.

Conclusion

Intravenous iron supplementation should be considered to treat IDA in children where oral administration has failed. The possible occurrence of systemic reactions emphasizes the need for very close medical supervision. Prospective studies involving larger population are needed to clarify the proper indications of intravenous iron, and to determine the safety and efficacy of parenteral iron therapy in children.

Authors' contributions: Conception and design: JR; Acquisition, analysis and interpretation of data:JR, TB, AĐ; Drafting the article JR, TB, AĐ; Revising it critically for important intellectual content: JR.

Conflict of interest: The authors declare that they have no conflict of interest.

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