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OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2019; 6(10):278-83

Research Article Doi: 10.36472/msd.v6i10.317

Efficacy and safety of intravenous iron sucrose treatment in children with iron deficiency anemia

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Abstract

Objective: The purpose of this study is to investigate the efficacy and safety of intravenous iron sucrose treatment in children with iron deficiency anemia who were unresponsive to or could not tolerate oral iron therapy.

Material and Methods: Among patients determined to have iron deficiency anemia, and were intolerant or noncompliant with oral iron therapy, 92 patients who have received parenteral iron therapy between the ages of 6 months and 18 years have been investigated retrospectively. Age, gender, patient complaints at application, dietary characteristics, accompanying diseases and treatment complications, and safety, tolerability, and adverse events have been assessed from the information obtained from patient files. Treatment efficiency was evaluated with hemoglobin (Hb), mean corpuscular volume (MCV) and ferritin results from the blood samples taken before treatment, at the second week of treatment and after two months.

Results: Mean age of patients was 12.5 ± 4.7 (age interval 1-17 years), and 21% was male while 79% was female. 72% of our patients were adolescents. From an etiological aspect, 56% of our patients was determined to have an iron-poor diet, 29% had functional menorrhagia, and 15% had chronic gastrointestinal system pathologies. Mean Hb, MCV and ferritin levels before and after treatment were found as: 7.72 ± 1.21 g/dl and 11.44 g/dl ± 0.68 g/dl; 63.2 ± 7.12 fL and 76.6 ± 3.81 fL; 3.87 ± 2.52 nmol/L and 57.94 ± 17.19 nmol/L, respectively ($p< 0.001$). 94% of patients were determined to have at least 2 g/dL (mean value 3.71 [range 1.6-6.3]) increase in their Hb levels. Anaphylaxis was observed in a patient who had a history of allergy despite applying premedication.

Conclusion: Parenteral iron therapy is an efficient and safe treatment among indicated patients.

Keywords: children, intravenous iron, iron deficiency anemia, iron sucrose

Introduction

Iron deficiency anemia (IDA) is still a common health problem in childhood around the world. While it has various reasons, nutritional IDA is the most important reason for anemia. Iron deficiency (ID) and IDA are among the top fifteen diseases all around the world with regard to global burden of disease. According to 2001 data of World Health Organization, 30% of children aged between 0-4 and 48% of children aged between 5-14 are anemic in developing countries (1-3). In various studies from our country performed on childhood, it was reported that the prevalence of IDA is between 15.2% and 62.5% (4-7).

Particularly in infancy and adolescence, the most common reason for IDA development is inability to meet the increased need for iron with nutrition. It is recommended to examine the presence of underlying bleeding, parasitosis or malabsorption disorders such as celiac disease in childhood and adolescence (1). Oral administration is primarily preferred as iron therapy since it is economic and has a low number of side effects. The use of 2-3 dose of drugs every day for two or three months is quite difficult for the child and the family, and problems in treatment compliance are common. Parenteral iron therapy can be applied upon intolerance to oral iron treatment, in cases requiring rapid recovery of anemia, and in malabsorptive-digestive problems such as celiac disease or inflammatory bowel disease. There is a small number of studies comparing parenteral and oral iron therapy for IDA due to nutritional deficiency in childhood, and there is a need for more studies in this subject. Iron supplements that have been released to the market in recent years have been safer, and have a relatively low number of adverse effects. However, it should be kept in mind that these adverse effects are serious (8).

Received 04-10-2019 **Accepted** 27-10-2019 **Available Online** 29-10-2019 **Published** 30-10-2019
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http://dx.doi.org/10.36472/msd.v6i10.317

Parenteral iron treatment is administered through intramuscular (IM) or intravenous (IV) route. Particularly after rapid infusion, findings such as allergy, anaphylaxis, low blood pressure, nausea, vomiting, and abdominal pain may be developed (9). There are no sufficient efficacy and adverse effect results on the literature for the use of IV iron in the treatment of iron deficiency anemia in childhood. Over recent years, parenteral iron preparations on the market (such as iron sucrose and ferric carboxymaltose) have been safer and had a very low number of adverse effects (10,11). The purpose of our study is to investigate the efficacy and safety of intravenous iron sucrose treatment in children with IDA who were unresponsive to or could not tolerate oral iron therapy.

Materials and methods

Setting and study population

Among patients who have applied to Bursa Dörtçelik Children's Hospital Pediatrics Clinic between dates April 01, 2013 – March 31, 2014, determined to have iron deficiency in the result of performed tests and who have received parenteral iron therapy due to intolerance and noncompliance against oral iron therapy; the clinical and laboratory characteristics of children between the ages of 6 months and 18 years were retrospectively investigated in our study. The study was approved by the local ethics committee. Before being included in the study, written informed consent was obtained from all parents or legal guardians of the patients.

The diagnosis of IDA was determined when red blood cell mass and hemoglobin concentration was -2 SD lower than values that were recognized to be normal according to age, gender, and physiological status. Red blood cell indices of MCH (<27 pg), MCHC (<30% units), RDW (>15 units) and ferritin <12 nmol/L were included among diagnostic criteria (9). Gynecological examinations, gastroscopy and/or colonoscopy were performed on necessary patients to determine the etiology of iron deficiency. Celiac antibodies were checked in patients with positive fecal occult blood results or determined to have delays in growth development parameters.

Iron treatment

Inability to tolerate oral iron therapy, not responding to oral iron administration after a sufficient period, continued blood loss and inflammatory bowel disease have been recognized as parenteral iron therapy indications (All patients have been using at least 2 different iron preparations 2-3 doses in a day or at 5-6 mg/kg/day dose for at least 3 months before being included in the study).

Daily IV iron level to be administered was determined as 50-200 mg. For 43 patients, it was observed that test dose was applied in the first infusion. In the treatment of patients, iron deficit was calculated and treated by using a 2-hour infusion of iron preparations, which were in ampoule form and contained ferric hydroxide sucrose drug substance, after reconstituting those with 100 ml 0.09% isotonic saline, at a maximum of 50 mg/day dose below 10 kg body weight, a single dose of 100 mg / day in infants, and 2 doses of 200 mg / day IV in older children.

Iron deficit is calculated by the following formulation (12):

$$\text{Iron Deficit} = \frac{(\text{Intended Hb level} - \text{Patient's Hb level})}{100} \times \text{Blood Volume} \times 3.4 \times 1.5$$

Efficacy and safety

Patients were examined with regard to age, gender, patient complaints at application, dietary characteristics, accompanying diseases and treatment complications. Hb, MCV, and ferritin results were examined retrospectively from blood samples taken before parenteral therapy and in controls at treatment day 14 and month 2. The patients whose Hb levels were increased 2 g/dL or higher in the post-treatment control were evaluated as ‘’benefited from treatment’’.

Statistical analysis

Characteristic data are presented as n (%) for categorical variables, and as mean ± SD or median (interquartile range [IQR]) for continuous variables, as appropriate.

Paired t-tests were used in order to compare parameters of our study before, during and after treatment.

All tests were two-tailed and p-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed by using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Mean age was determined as 12.5 ± 4.7 (range 1-17 years) in a total of 92 patients included in our study. Nineteen (21%) patients were male, while 73 was (79%) female. 79% of our patients were in adolescence. From an etiological aspect, 56% of our patients was determined to have an iron-poor diet, 29% had functional menorrhagia, and 15% had chronic gastrointestinal system pathologies (7% chronic gastritis, 6% celiac disease, 2% ulcerative colitis) (Table 1).

Table 1. Causes of iron deficiency anemia

Condition	n
Nutritional iron deprivation	51
Functional menorrhagia	26
Gastritis due to *Helicobacter pylori*	7
Celiac disease	6
Ulcerative colitis	2
Total	92

Efficacy

The number of iron sucrose infusions per patient ranged from 3 to 8 (median: 5), the individual doses from 100 mg to 200 mg (median: 200 mg), and the total doses from 200 mg to 1200 mg (median: 1000 mg).

Mean Hb blood level before treatment was 7.72 ± 1.21 g/dl (range 5–10.1 g/dl). It was observed that Hb levels increased to 10.0 ± 0.78 g/dl (range 8.0–11.8 g/dl) at post-treatment day 14 and to 11.44 g/dl ± 0.68 g/dl (range 9.2–13.0 g/dl) at post-treatment month 2. The rise in Hb blood

http://dx.doi.org/10.36472/msd.v6i10.317

level was found to be statistically significant both 14 days and 6 months after starting iron therapy ($p < 0.001$) (Figure 1). As treatment response, at least 2 g/dL (mean value 3.71 ± 1.09 [range 1.6-6.3]) increase was determined in 94% of patients considered as having benefited from treatment.

Mean MCV levels were 63.2 ± 7.12 fL (range 43.4-81.7 fL) before treatment. It was observed that MCV levels were elevated to 72 ± 5.38 fL (range 53-82 fL) at day 14 and 76.6 ± 3.81 fL (range 65-87 fL) at the end of 2 months. A statistically significant difference was determined between levels measured before treatment and during treatment ($p<0.001$). Serum ferritin level prior to therapy was low in all patients: mean 3.87 ± 2.52 nmol/L (range 1–12.9 nmol/L). The serum ferritin level rose to a mean of 44.9 ± 14.58 nmol/L (range 24–88 nmol/L) after 14 days, and 57.94 ± 17.19 nmol/L (range 29–102 nmol/L), after 2 months.

The rise in ferritin level was found to be statistically significant both 14 days and 6 months after starting iron therapy ($p < 0.001$) (Figure 2).

Safety

Two patients had short-term chest pain following iron infusion. Physical examination of these patients, saturation, electrocardiogram and cardiac enzymes were determined to be normal. It was found out that these 2 patients were followed up in pediatric psychiatry department due to anxiety. Despite applying premedication, anaphylaxis was observed in a patient who had a history of allergy. Two patients were observed to have swelling and discoloration on vascular access secondary to drug extravasation. No venous thrombosis was observed in any of the patients

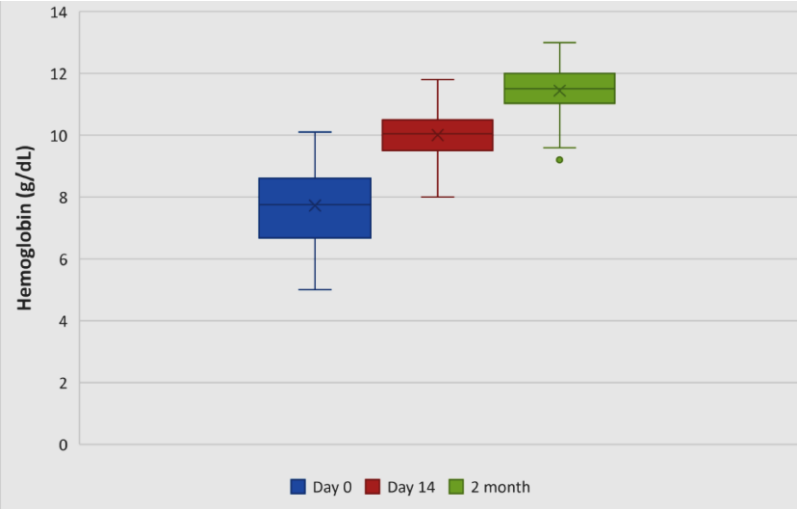

Figure 1. Differences in mean hemoglobin levels measured on day 0, day 14 and 2 month after starting intravenous iron therapy. The rise in hemoglobin blood level was found to be statistically significant both 14 days and 6 months after starting iron therapy ($p < 0.001$).

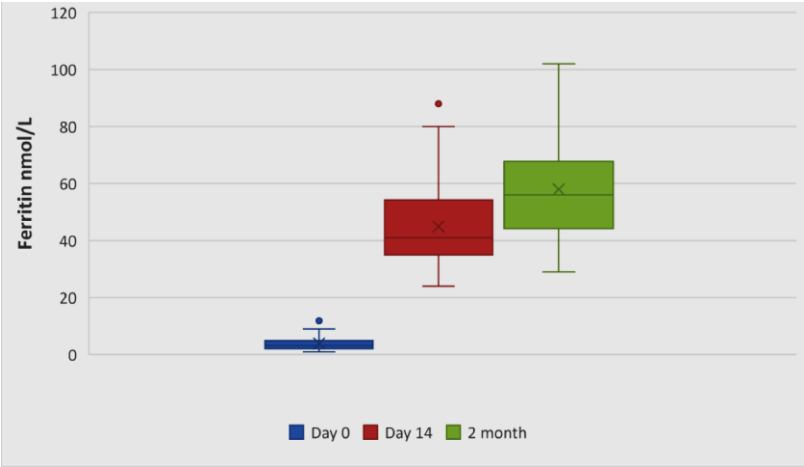

Figure 2. Differences in mean ferritin levels measured on day 0, day 14 and 2 month after starting intravenous iron therapy.The rise in ferritin level was found to be statistically significant both 14 days and 6 months after starting iron therapy ($p < 0.001$).

Discussion

Iron deficiency is the most common nutritional deficiency around the world, and it is an important public health problem particularly in developing countries. It is most commonly observed in childhood at infancy and in menstruating adolescents, however, all children with increased growth rate whose needs are not met sufficiently are under risk (8).

Since IDA is known to affect physical and neurocognitive functions in particular, it should be recognized and treated in childhood (13). In our study, 56% of cases had deficiencies in their diet that posed a problem with regard to anemia. In compliance with literature, nearly all of cases were determined to have significant deficiencies in red meat consumption (14).

It is also known that adolescents will develop IDA if increased iron need due to rapid growth is not met. The rate of adolescents with IDA in our study group were determined to be 79%, and as stated in the literature, it can be said that adolescents are under the risk of ID (10). Also, chronic blood loss is commonly observed in the etiology of this group. Functional menorrhagia was determined to be 36% in this group in our study, and it attracts attention as an important cause.

Oral administration is primarily preferred as iron therapy since it is economic and has a low number of side effects. Parenteral iron therapy can be applied upon intolerance to oral iron treatment, in cases requiring rapid recovery of anemia, and in malabsorptive-digestive problems such as celiac disease or inflammatory bowel disease.

In the study of Crary et al. (15), mean Hb increase in patients who cannot tolerate oral iron therapy was 0.05 (-1.0 - 1.0) g/dL with oral therapy, while it was 3.1 (0.8 - 7.6) g/dL with IV iron sucrose. In patients with chronic blood loss, mean Hb increase was determined as 0.65 (-1.4 - 5.7) g/dL with oral treatment while it was 1.9 (0.2 - 6.6) g/dL with IV iron sucrose. In the study of Pinks et al. (16) on the efficacy and safety of intravenous iron sucrose treatment in pediatric patients with IDA, mean Hb level was 7.43 g/dL before treatment, while it was 9.27 g/dL on day 14 and was determined to increase to 12.4 g/dL at month 6. The ferritin level, which was 3.5 nmol/L before treatment, was also determined to increase to 60 nmol/L on day 14 following treatment, and it returned to normal limits (16-250 nmol/L) on month 6, decreasing to 27.99 nmol/L.

In their efficacy and safety study of parenteral iron (ferric carboxymaltose and iron sucrose) on children with inflammatory bowel disease, Papadopoulos et al. (17) have determined 2.5 g/dl mean Hb increase and observed side effects of urticaria rash in all three cases. It was determined in our study that 94% of our patients benefited from treatment. Mean 3.71 ± 1.09 g/dl Hb increase was observed, and the efficacy of parenteral iron therapy was statistically determined.

Being first used on 1930s in only rare cases, parenteral iron (iron oxyhydroxide complex) 22 treatment was observed to have very serious adverse effects (18,19). Bioavailability was increased with a high- molecular weight iron dextran developed in 1950s, and allergic reactions were observed at 0.6%-2.3% rate. Later, while ferric gluconate was safer compared to iron dextran, the incidence of anaphylaxis could not reach the intended level, remaining at 0.04% (20-23).

With the clinical use of iron sucrose in 2000s, the incidence of anaphylaxis was reduced to 0.002%. The biggest disadvantage of iron sucrose is the low maximum single administrable dose, and this causes numerous individual infusions in order to reach therapeutic dose. Lastly, ferric carboxymaltose was released in Europe in 2007, licensed for patients older than age 14. 1000 mg dose of iron can be administered in a single application and it can be applied for 15-60 minutes at a relatively fast manner without requiring a test dose, therefore hospitalization period and cost can be reduced (24).

In the study of Pinsk et al. (16) on a group of 45 pediatric patients, it was reported that 1 patient experienced temporary hypotension half an hour after starting IV iron sucrose administration that has recovered after pausing the treatment, and 2 patients experienced discoloration without pain around the vascular access intervention area due to drug extravasation that subsided in 24 hours.

Crary et al. (15) has reported in their IV iron sucrose study performed on 38 pediatric patients that 6 patients experienced adverse effects; 1 of which was headache, 2 were abdominal pain, 1 was temporary hypotension, 1 was vasovagal syncope, and a 15-year-old patient was reported to experience an anaphylactoid reaction 10 minutes into the infusion with diffuse pain on his body, swelling on his face, weak pulse and hypotension and it was reported to alleviate with epinephrine, diphenhydramine, and methylprednisolone.

Meanwhile, Mantadakis et al. (12) have reported that 3 patients developed injection site extravasation and 1 patient had a temporary change in taste in their study performed on 12 pediatric patients. Papadopoulos et al. (17) have stated that among 35 patients receiving ferric carboxymaltose, 2 patients had rash after completing the first infusion, and one case had an urticarial rash that started in the first 30 minutes of infusion and an allergic reaction accompanied by hypotension that recovered rapidly with IV chlorphenamine.

Premedication with antihistamines (diphenhydramine) was reported to have caused the majority of perceived reactions to IV iron in one large cohort (25). Patients with asthma or drug allergies should be routinely pre-medicated with methylprednisolone or hydrocortisone prior to IV iron infusion. In our study, anaphylaxis was observed in a patient who had a history of allergy despite applying premedication, and 2 patients were determined to have swelling and discoloration on vascular access secondary to drug extravasation. No venous thrombosis was observed in any of the patients.

Compared to the patient number in literature studies, our study group seems to have a valuable number of patients. It was observed in our study that parenteral iron administration rapidly recovered the general symptoms of

anemia in suitable cases with regard to parenteral iron therapy indications in particular, and the intended increase was attained in 94% of patients with this treatment.

Since it provided rapid symptomatic recovery and improvement in quality of life in patients with IDA symptoms even while treatment is continued, it can be seen that parenteral therapy is a good option. Based on these reasons, we consider that the application of parenteral therapy would be right in indicated cases.

In the result of our study, we would like the state that nutritional ID is still an important etiological factor and emphasize the importance of evaluating gastrointestinal system in chronic blood loss, and particularly in girls, gynecological evaluation against functional menorrhagia. Contrary to usual belief, it can be said that the risk of developing anaphylaxis is lower in pediatric age group compared to adults.

Our study has contributed to the limited number of pediatric studies on literature. Nevertheless, in order to avoid the most important limitation of our study, which is the possibility of misleading results residing in the nature of every retrospective study, prospective planning of future studies is considered to be valuable.

Conclusion

Parenteral iron therapy is quite efficient in the treatment of IDA when used in suitable cases. Contrary to popular belief, adverse effects are lower and milder in pediatric patient group compared to adults. The application of parenteral iron therapy is efficient and safe in children who cannot tolerate oral iron therapy, do not benefit from oral iron therapy or have chronic diseases such as celiac disease which disrupt iron absorption.

Acknowledgement: No

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: EGK, MFK, BO; Research concept and design, research the literature, laboratory examinations, preparation of the article**. MFK;** Statistical analyzes. **EGK;** Revision of the article.

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