ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Is Intravenous Iron Treatment in Pediatric Patients Safe and Effective Enough?

Pediatrik Hastalarda İntravenöz Demir Tedavisi Yeterince Güvenli ve Etkili mi?

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Abstract

Introduction: Iron deficiency anemia (IDA) is the most common hematological disease among infants and children. Although most of the children with IDA are treated with oral iron preparations, intravenous (IV) iron is an alternative for children with severe IDA who have difficulty in adhering to or absorbing oral iron. In this study, the reasons of IDA in patients treated with IV iron and the effectivity and safety of iron sucrose preparations in pediatric patients were evaluated.

Materials and Methods: The medical records of children received IV iron sucrose at a pheripheral hospital between June 2014 and June 2017 were reviewed retrospectively. The IDA patients who are unresponsive to oral iron or whose hemoglobin (Hb) <7 g/dL and received IV iron treatment were evaluated for the reasons of anemia, the efficacy and safety of IV iron treatment. Before and after iron sucrose infusion laboratory results were compared. All records were reviewed for serious side effects and allergic reactions.

Results: A total of 33 patients, aged between 3-18 years were enrolled into the study. While 58% of the patients who received IV iron treatment had inadequate consumption of iron, 24% had malabsorption. In the initial evaluation Hb levels of the patients were 3.2-7.8 (6.54±1.06) g/dL, (mean corpuscular volume) MCV was 59.18±6.66 fL and ferritin was 1.87±1.34 μg/L, the mean post-treatment Hb was 11.39±1.51 g/dL, MCV was 76.06±7.59 fL and ferritin was 54.79±15.64 μg/L. No serious side effects were seen.

Conclusion: The use of IV iron sucrose in pediatric patients with IDA leads to significant increase in Hb and reduces erythrocyte suspension transfusion and is an effective and safe method for iron treatment.

Keywords
Iron deficiency anemia, intravenous treatment, effectivity, safety

Öz

Giriş: Demir eksikliği anemisi (DEA) çocukluk çağında en sık görülen hematolojik hastalıktır. DEA olan çoğu çocuk oral demir ile tedavi edilse de, tedavi uyumu olmayan, emilim bozukluğu olan ağır DEA'lı çocuklarda intravenöz (İV) demir uygulaması bir tedavi alternatifidir. Bu çalışmada İV demir tedavisi uygulanan çocukların anemi nedenleri, tedavi etkinliği ve güvenliği incelenmiştir.

Gereç ve Yöntem: Haziran 2014-Haziran 2017 yılları arasında anemi nedeni ile çocuk hekimi tarafından çocuk hematoloji polikliniğine yönlendirilen ve İV demir tedavisi uygulanan olguların dosyaları retrospektif olarak incelenmiştir. Oral demire yanıt vermeyen veya hemoglobini (Hb) <7 g/dL olan ve İV demir tedavisi uygulanan DEA hastalarının anemi nedenleri, İV demir tedavisinin etkinliği ve güvenliği açısından değerlendirildi. Demir sükroz infüzyonu öncesi ve sonrası laboratuvar sonuçları karşılaştırıldı. Tüm kayıtlar ciddi yan etkiler ve alerjik reaksiyonlar açısından gözden geçirildi.

Anahtar kelimeler
Demir eksikliği anemisi, intravenöz tedavi, etkinlik, güvenlilik

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Bulgular: Çalışmaya 3-18 yaş arası toplam 33 hasta alındı. İV demir tedavisi alan hastaların %58'inde yetersiz demir alımı varken, %24'ünde malabsorbsiyon vardı. İlk değerlendirmede hastaların Hb düzeyleri 3,2-7,8 (6,54±1,06) g/dL, ortalama korpüsküler hacim (MCV) 59,18±6,66 fL ve ferritin 1,87±1,34 μg/Ll iken, tedavi sonrası 4-6. haftada bakılan Hb 11,39±1,51g/dL, MCV 76,06±7,59 fL ve ferritin 54,79±15,64 μg/L idi. Ciddi bir yan etki görülmedi.
Sonuç: DEA'lı çocuklarda İV demir tedavisi Hb'de hızlı artışa yol açar ve eritrosit süspansiyonu transfüzyon ihtiyacını azaltır. Güvenli ve etkili bir tedavi yöntemidir.

Introduction

Iron deficiency anemia (IDA) is the most common hematological disease among infants and children. Especially in developing countries IDA is frequently seen. Although iron deficiency affects 9% of toddlers and up to 16% of adolescent girls and 3% of all pediatric patients in American studies (1,2), iron deficiency is estimated up to 30-78% and IDA is estimated to 5.6-12.5% in different age groups in comprehensive studies performed in Turkey (3,4).

Iron deficiency can be caused by multiple factors including insufficient iron intake, decreased iron absorption and gastrointestinal blood loss from inflammatory bowel disease or chronic use of nonsteroidal anti-inflammatory drugs. In addition, cow's milk, which is a poor source of iron, can cause occult blood loss and inhibit the absorption of iron from other food sources (5). Adolescent girls with menorrhagia are also at a high risk of IDA.

As inadequate consumption of iron causes neurodevelopmental consequences, the rapid and effective treatment of IDA is mandatory. Nearly all of the children with IDA are treated with oral iron preparations. After starting the oral iron therapy, the increase of reticulocyte count is seen as early as 3 days, while improvement of hemoglobin (Hb) concentration is detected later. Hb normalization is a slow process, taking up to 6 months after the start of therapy (6). Although oral iron therapy is cheap, safe, and effective at correcting IDA, it is not well tolerated by some patients and in a subset of patients, it is insufficient. Patients in whom the blood loss is more than the intestinal ability to absorb iron (e.g. intestinal angiodysplasia, malabsorption, von Willebrand's disease..) may develop IDA refractory to oral iron supplementation. These patients are the most challenging to manage and they may have required multiple and frequent blood transfusions and suffer end-organ damage as a result of their refractory anemia (7).

In this study, the reasons of IDA in patients treated with intravenous (IV) iron in a peripheral hospital and the effectivity and safety of iron sucrose preparations in pediatric patients were evaluated.

Materials and Methods

The medical records of 33 children who received IV iron sucrose at a single center between June 2014 and June 2017 were reviewed retrospectively. The patients who aged between 3-18 years, were referred to pediatric hematology department with oral iron unresponsive or Hb <7 g/dL IDA and received IV iron treatment were evaluated for the reasons of anemia, the efficacy and safety of IV iron treatment. Firstly, the patients were evaluated for the etiology of anemia. The patients who were diagnosed as IDA were included in the study. The unresponsiveness was considered as using oral iron formulations appropriately at least for three months, but neither Hb nor reticulocyte count increase was seen. The patients who had diagnosis of hemoglobinopathy, chronic renal insufficiency or anemia of chronic disease were excluded.

The hospital's electronical medical records were used to obtain laboratory results pre-IV and post-IV iron sucrose including markers of anemia such as Hb and mean corpuscular volume (MCV), serum iron, ferritin, total iron binding capacity, and percent of iron saturation, Vitamin B12, folate and the reasons of iron deficiency such as anti-gliadin IgA and G, anti-endomysium IgA and IgG and occult blood test in stool, macroscopic and microscopic evaluation of stool for parasitic infections. Mean (when normally distributed) or median values of laboratory parameters were recorded. The post-IV treatment evaluations were performed 4-5 weeks after the initiation of the treatment.

For IV iron sucrose, the following calculation was used to determine the total iron deficit for initial repletion: total cumulative dose (mg) = [target Hb (12 g/dL) - actual Hb] × weight (kg) × 0.24 + [15 × weight (kg)]. To prevent adverse reactions, the maximum

daily dose of iron sucrose was limited to 200 mg/day or 4 mg/kg/day. It was diluted in 100 mL of normal saline and administered for 1 hour on each day (8). IV iron treatment was applied 2 times a week in either outpatient or inpatient clinic until the total cumulative dose was replaced.

Before and after iron sucrose infusion laboratory results were compared. HPLC was performed to 4 suspected patients after IV iron treatment. Fifteen patients with hemorrhage history were also evaluated for hemorrhagic diathesis. Eight patients were referred to pediatric gastroenterology and endoscopy - colonoscopy was performed.

All records were also reviewed for serious side effects and allergic reactions.

The study protocol was approved by the Institutional Ethics Committee of Balıkesir University, approval number: 2017/148, date: 13.12.2017. Informed written consent was obtained before enrolling children into the study.

Statistical Analysis

The paired t-test is used to assess statistical significance for all parameters except ferritin. As the data for ferritin were not normally distributed, the Wilcoxon signed rank test and interquartile range is used.

Results

A total of 33 patients who had IV iron treatment between June 2014 and June 2017 at Balıkesir Ataturk Government Hospital were enrolled into the study. The patients were aged between 3-18 (11.09±4.67) years. Seventeen of the patients were girls. The demographic data are shown in Table 1. The baseline Hb levels was lower than 7g/dL in nineteen (58%) of the patients and severe anemia was developed due to inadequate consumption of iron (four patients had also Thalassemia trait, one patient had intolerance to oral iron preparations and two patients had Pica). Iron unresponsiveness was seen in fourteen patients. While eight (24%) of the patients had malabsorption (one patient had Crohn disease and seven patients had Celiac disease), four (12%) of the patients had abnormal uterine bleeding and one of the patient had Von Willebrand's disease. One patient had total gastrectomy due to perforation in childhood.

While 8 patients had both vitamin B12 and iron deficiency, 2 patients had folate and iron deficiency. None of the patients had the deficiency of all and the combined deficiency was not related to malabsorption ($p>0.05$). The B12 and folic acid treatments were given during and after IV iron treatment.

The initial evaluation Hb of the patients were 3.2-7.8 (6.54±1.06) g/dL, MCV was 59.18±6.66 (50-83) fL and ferritin was 1.87±1.34 (0-5) μg/L. The pre and post treatment laboratory tests were shown in Table 2. The control mean Hb elevation at the first week of treatment was 2.3±1.5 g/dL. The mean time period of taking pre and post-treatment laboratory tests was 30±3.4 days. The comparison of the pre and post-treatment Hb, MCV and ferritin were shown in Table 2. The mean post-treatment Hb was 11.39±1.51 g/dL, MCV was 76.06±7.59 fL and ferritin was 54.79±15.64 μg/L. The average number of IV iron doses received was 5.6.

Only one patient whose Hb was below 5 (3.2) g/dL, had received only one unite of packed red blood cell and IV iron treatment was started when his post-transfusion Hb was 5.7 g/dL. This patient's pre-transfusion ferritin level was below 1 μg/L and serum iron was 4 μg/L. Any other erythrocyte suspension was needed.

One patient had fever during iron infusion. By giving antipyretic and tapering the infusion rate of iron, no problem was seen. One patient had

Table 1. Demographic characteristics of the patients receiving parenteral iron therapy

Ages (years)	N (%)
3-5	5 (16)
6-10	9 (27)
11-15	10 (30)
16-18	9 (27)
Sex	
Girls	17 (51.5)
Boys	16 (48.5)
Diagnosis	
Inadequate consumption	19 (58)
Malabsorption	8 (24)
Total gastrectomy	1 (3)
Dysfunctional uterine bleeding	4 (12)
Von Willebrand's disease	1 (3)

Table 2. Laboratory characteristics of patients before and after parenteral iron therapy			
	Pre treatment	Post treatment	p
Hemoglobin (g/dL)	6.54±1.06 (3-7.8)	11.39±1.51 (8.2-13.3)	0.00
MCV (fL)	59.18±6.66 (50-83)	76.06±7.59 (58-93)	0.00
RDW (%)	20.63±6.62 (17-48)	12.32±5.75 (11-23)	0.00
Fe (μg/dL)	16.94±10.37 (4-32)	35.3±8.8 (24-55)	0.00
Transferrin saturation (%)	5.3 (0-13)	42.1 (25-55)	0.00
Ferritin (μg/L)	1.87±1.34 (0-5)	54.79±15.64 (22-95)	0.00
B12 (nmol/L)	390±203 (101-1099)	N/A	-
Folate (μg/L)	5.48±2.59 (1-11)	N/A	-
MCV: Mean corpuscular volume, RDW: Red cell distribution width, B12: Vitamin B12, Fe: Iron			

thrombophlebitis after the third day of iron infusion. Neither any other adverse effects, nor allergic reactions were seen.

Discussion

Iron deficiency is the most widespread nutritional disorder in the World. Traditionally, oral iron therapy in the form of ferrous salts, carbonyl iron, and ferric protein succinate or iron polysaccharide combinations is the recommended treatment for IDA (9-13). Whatever is chosen, oral iron therapy requires good patient compliance for several months in order to be effective. Moreover, the most widely used and cheaper oral iron products (14), are less well tolerated, and in situations where IDA is due to gastrointestinal bleeding and menorrhagia, iron loss may be greater than the oral iron supply. The same as the general approach oral iron preparations are the first choice in our center. As few patients needed IV iron treatment, the effectiveness of iron sucrose on iron studies in addition to describing Hb increase after infusion in children with severe IDA and/or unresponsive to oral iron preparations were planned to evaluate in this study.

IV iron is an infrequently used therapeutic alternative to oral iron for the treatment of IDA in children. By far, the most common pediatric indications for IV iron in everyday clinical practice are unresponsiveness, intolerance or incompliance to oral iron therapy, malabsorption, rapid need of anemia correction, heavy menstrual bleeding in adolescent females (15).

Although IV iron was given for a variety of reason in this study, the most common reason was inadequate iron consumption, followed by malabsorption. Also as the initial Hb level of our cohort was 6.54±1.06 (3.2-7.8) g/dL, IV iron was given for quick correction of anemia and reduction erythrocyte suspension transfusion. The IV iron preparations that are being used in Turkey are iron sucrose, sodium ferric gluconate and ferric carboxymaltose (not yet approved for pediatric use). These products are similar in terms of safety profile but differ in the content and frequency of the doses administered (16). While a typical therapeutic course of iron sucrose requires 5-10 injections of 100-200 mg doses of each and multiple infusions are required to replenish iron stores, iron carboxymaltose allows the administration of high doses of iron over a limited time (17). As iron sucrose was the only IV preparation in the hospital during the study period, iron sucrose was used in our study, similar to the majority of pediatric studies (18-20). Considering the negative effects on neurodevelopment associated with IDA, the repletion of the iron stores of these children safely and immediately is important. Hb increment effect of IV iron formulations was shown in few studies and 1.56 to 4.8 g/dL increase was reported in one to sixteen weeks (21-27). Similarly, in our study the evaluation which was performed after the first week of IV iron therapy initiation, there was 2.3±1.5 g/dL improvement in Hb levels. Although IV iron therapy is more expensive than oral iron, it might lead to faster iron repletion in patients with severe anemia allowing for fewer doctor visits, less frequent laboratory tests, less time out of school, decreased need for packed red blood cell transfusions, and potentially lower overall costs. The presence of a safe IV alternative preparation of iron is necessary because there are many pediatric patients who cannot tolerate or do not adhere to oral formulations.

Also as the weights of children are smaller than adults, the measurement of iron deficiency is lower and high dose therapy can cause hemosiderosis in children. The correct calculation of iron deficiency and close follow up is important.

Although the current pediatric experience with IV iron administration for children with IDA is limited, IV iron is both effective and safe in children (11-13,16-27). Few side effects were seen during IV iron infusions in our patients. In a review and meta-analysis performed by Avni A et al. (22) IV iron therapy is not associated with an increased risk of SAEs or infections. Infusion reactions are more pronounced with IV iron.

As it was a retrospective study, the patients were neither paid nor reported.

The effectivity and the safety of IV iron in severe IDA is pointed out in this study. Not only the Hb levels were significantly elevated, but only two minor adverse events were seen. While 8 patients with B12 deficiency were also given oral B12 preparations, 2 patients with folic acid deficiency were given oral folic acid preparations during and after IV treatment.

Study Limitations

Limitations of our study were being retrospective and the reticulocyte count during the study was not included. There is a scarcity of literature in support of IV iron versus oral iron in the medical management of severe anemia and details of administration (doses, interval, factors to assess when the next dose is needed, etc.) are lacking. The study was performed by hematologists and pediatricians because no gastroenterologist was present in the hospital during the follow up. The comparison of the long-term cost effectiveness of using oral iron or IV iron sucrose should be evaluated in more comprehensive studies in future.

Conclusion

The use of IV iron sucrose in pediatric patients with IDA is safe and leads to significant increase in Hb and reduces erythrocyte suspension transfusion.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of Balıkesir University, approval number: 2017/148, date: 13.12.2017.

Conflict of Interest: No conflict of interest was declared by the authors.

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