



## Efficacy and Safety of Intravenous Iron Sucrose Therapy in a Group of Children with Iron Deficiency Anemia

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**Key words:** intravenous iron sucrose, anemia, iron deficiency

### Abstract

**Background:** Iron deficiency is the most common single cause of anemia worldwide. Treatment consists of improved nutrition along with oral, intramuscular or intravenous iron administration.

**Objectives:** To describe the efficacy and adverse effects of intravenous iron sucrose therapy in a group of children with iron deficiency anemia who did not respond to oral iron therapy.

**Methods:** We conducted a prospective investigation of 45 children, aged 11 months to 16 years, whose oral iron therapy had failed. The children attended the Pediatric Day Care Unit where they received intravenous iron sucrose infusion.

**Results:** Forty-four of the 45 patients were non-compliant. Nine had *Helicobacter pylori* gastritis and 16 patients suffered from intestinal malabsorption from different causes. Before treatment, the blood mean hemoglobin concentration was 7.43 g/dl (range 5–10.1 g/dl). Fourteen days after treatment it increased to 9.27 g/dl (SD 1.23) and 6 months later to 12.40 g/dl (SD 1.28). One patient demonstrated a severe side effect with temporary and reversible reduced blood pressure during treatment.

**Conclusions:** These preliminary data suggest that administration of intravenous iron in pediatric patients is well tolerated and has a good clinical result, with minimal adverse reactions.

*IMAJ 2008;10:335–338*

For Editorial see page 372

Iron deficiency is the most common cause of anemia due to nutritional deficiency [1,2]. In industrialized countries 17% of children under 5 years old suffer from iron deficiency anemia [3]. A recent study from Israel showed a prevalence of 15.5% in infants aged 9–18 months [4].

Many factors predispose children to iron deficiency anemia, including nutritional deprivation, intestinal malabsorption and blood loss. Another cause is ingestion of intestinal iron absorption inhibitors, such as phytates or cow's milk protein, which may lead to iron deficiency [5].

The treatment of iron deficiency anemia consists of improved nutrition along with oral, intramuscular or intravenous iron administration. Currently, several intravenous iron preparations are available for use, including iron dextran, iron gluconate and iron sucrose. Treatment with these intravenous iron prepara-

tions leads to an increase in hemoglobin blood levels and to restoration of iron stores [6]. However, the use of iron dextran is associated with side effects that include anaphylactic reactions (immune and dose-related) in approximately 1% of treated patients [7,8]. In addition, serum iron and ferritin blood levels remain significantly elevated for a long time after iron dextran administration [9]. The administration of iron gluconate is also associated with adverse effects, but these are usually mild and no fatal allergic reaction following the use of this preparation has been reported [10]. The use of iron gluconate or iron sucrose has fewer side effects compared to iron dextran [10]. In fact, iron gluconate was successfully administered to patients who previously had shown severe reactions, including anaphylaxis, to iron dextran [11]. In contrast, iron sucrose treatment is effective [12] and may be given safely to predialysis and hemodialysis patients with or without erythropoietin therapy [13–15]. Pregnant women have also been treated with iron sucrose without untoward effects [16].

We conducted a prospective study in which infusions of iron sucrose were administered to pediatric patients with iron deficiency anemia who failed to respond to oral iron treatment.

### Patients and Methods

The study was approved by the local ethics committee of the Ben-Gurion University, Beer Sheva. The parents of the patients participating in this study signed written informed consent forms.

The diagnosis of iron deficiency was defined as hemoglobin level lower than 2 standard deviations below the normal 15.5% blood level corrected for age. Also required for the diagnosis was a ferritin level below 16 ml/L and red blood cell distribution width > 15. Non-compliance in children was defined as a child not taking iron treatment, administered in the form of at least two different oral preparations, for a minimum period of 3 months. The oral preparations that were administered to the patients were polymaltose iron complex, ferrous gluconate, ferrous lactate or ferrous sulfate at a dose of 6–7 mg/kg/day of elemental iron given two to three times daily.

Forty-five children (23 males and 22 females) aged 11 months to 16 years (average age 6 years 7 months) with iron deficiency anemia were treated in the pediatric day care unit. Twenty-five of them were Bedouin Arabs and 20 were Jewish. All patients were initially treated with oral iron for at least 3 months, except for one patient who suffered from short gut syndrome and was given intravenous iron as the initial treatment. Forty-four patients did not receive the oral iron treatment and thus were defined as non-compliant.

A standard prospective protocol was applied to all patients as follows: A complete medical history leading to the iron deficiency was obtained [Table 1]. The following laboratory tests were performed: sedimentation rate (by Westergreen method), serum ferritin (Beckman, UK), serum iron, complete blood count, including blood smear and reticulocyte count, serology for celiac disease using immunoglobulin A-anti-endomysial antibody (ImmuGLO, USA), immunoglobulin levels (Beckman coulter), and liver and kidney function tests. Stool was examined for the presence of parasites and blood.

#### Iron treatment

Iron was administered intravenously as iron sucrose complex (Venofer, Vifor, Switzerland) according to the protocol provided by the manufacturer, in the pediatric day care unit. Venofer is supplied in ampules containing 100 mg of elemental iron in 5 ml. The total amount of iron administered was calculated according to the patient's weight and hemoglobin using the following formula [17]:

$$\frac{\text{Normal hemoglobin for age} - \text{initial hemoglobin}}{100} \times \text{blood volume (ml)} \times 3.4 \times 1.5$$

Where 3.4 converts grams of hemoglobin into milligrams of iron and factor 1.5 provides extra iron to replace depleted tissue stores [18].

#### Daily dosage

Daily dosage was calculated as 5 mg Fe<sup>+++</sup> per kilogram per day. The number of days was calculated by dividing the total dose by the daily dose. The iron preparation was diluted to 1 mg Fe<sup>+++</sup> in 1 ml of NaCl 0.9%, and administered at an infusion rate of 1–1.3 ml/minute three times a week. All patients underwent a test where a quarter of the dose that was planned for the first infusion was administered at a rate that did not exceed 0.5 ml/minute [19].

#### Follow-up tests

Hemoglobin level, reticulocyte count and ferritin level were determined immediately before the iron administration, 14 days after the first iron dose and 6 months following completion of therapy. Transferrin saturation and serum iron level were determined before and one day after iron administration. Liver function tests were conducted before and at the end of treatment.

#### Statistical analysis

The data were collected and analyzed by the SPSS 11 for Windows software package. To assess the effect of changes in

hemoglobin concentration and ferritin levels, comparisons were used for hemoglobin and ferritin concentrations between samples. Paired *t*-tests were performed to compare between the groups. *P* < 0.05 was considered significant in all comparisons.

## Results

The basic conditions leading to the iron deficiency in 45 patients are listed in Table 1

#### Hemoglobin concentration

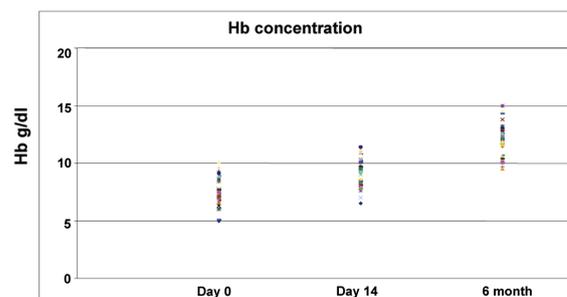
Mean hemoglobin blood level before treatment was 7.43 g/dl (range 5–10.1 g/dl) (SD = 1.21). After 14 days of treatment it increased to 9.27 g/dl (range 6.4–12.8 g/dl) (SD = 1.23) and after 6 months reached 12.4 g/dl (SD = 1.28) [Figure 1]. The rise in hemoglobin blood level was statistically significant both 14 days and 6 months after starting iron therapy (*P* < 0.000).

#### Ferritin

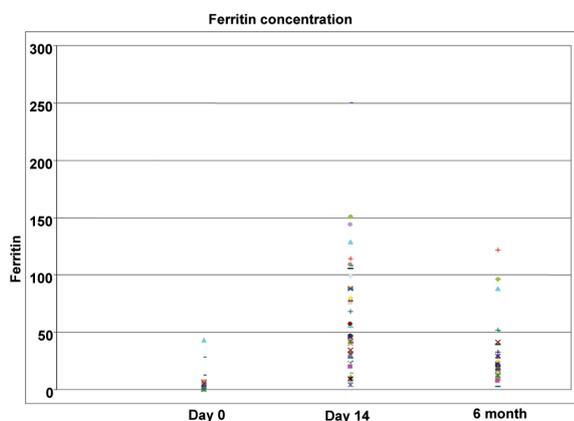
Serum ferritin level prior to therapy was low in all patients: mean 3.5 nmole/L (SD = 7.55), (normal range 16–250 nmole/L). The serum ferritin level rose to a mean of 60 nmole/L (SD = 47.73) after 14 days (*P* < 0.000) and returned to normal, 27.99 nmole/L (SD = 25.55), after 6 months. Despite the drop, the difference between the level before therapy and 6 months after therapy is still statistically significant (*P* < 0.000) [Figure 2].

**Table 1.** Causes of iron deficiency anemia in our patient group

Condition	No. of patients
Nutritional iron deprivation	20
Gastritis due to <i>Helicobacter pylori</i>	9
Celiac disease	5
Stool parasites (recurrent giardia lamblia)	4
Crohn's disease	2
Chronic diarrhea	2
Milk allergy	2
Short gut syndrome	1
Total	45



**Figure 1.** Hemoglobin blood levels (g/dl) on day 0, day 14 and 6 months following intravenous iron infusion.



**Figure 2.** Serum ferritin concentration (nmol/L) on day 0, day 14 and 6 months following intravenous iron infusion.

### Side effects

One patient experienced transient hypotension and vomiting half an hour after the initiation of intravenous iron sucrose infusion, which resolved after discontinuation of the drug. Two patients suffered from drug extravasation, with discoloration near the port of entry but no pain, which resolved within 24 hours. No other adverse effects were reported by the patients or their families. No biochemical abnormalities were noted during and in the follow-up period in any of the patients. On the day after the first iron dose, blood iron oversaturation was detected with serum iron above 150% saturation in three patients, which disappeared after lowering the dose on the following day.

### Discussion

Iron deficiency anemia is a very common problem in the pediatric population and is usually treated by oral iron administration. Most patients tolerate the therapy well. However, a number of patients fail to respond to oral iron treatment. In our patients the most common reason for oral treatment failure was lack of compliance [Table 1], followed by malabsorption due to various reasons. For these patients, intravenous iron sucrose treatment is recommended. Two patients who responded only partially to the treatment were found to have concomitant beta-thalassemia minor. In our study, nine patients (20%) suffered from *H. pylori* gastritis, a well-known cause for iron deficiency anemia [20]. *Helicobacter pylori* gastritis should be treated concurrently with iron supplementation.

Very few studies on intravenous iron supplementation in children have been published. Iron dextran was found to be effective when given to children with inflammatory bowel disease. Nevertheless, 14% of these patients developed immediate hypersensitivity reactions, which fortunately were not life threatening [21]. Iron sucrose was found to be more effective than oral iron in restoring postoperative hemoglobin following spinal surgery in children [22], or in rapidly increasing hemoglobin concentration in pediatric candidates for elective surgery [23]. Intravenous iron

sucrose may be safely administered to preterm infants. However, the small number of patients in the study precludes exact statistical analysis [24].

The blood ferritin level was a dependable marker for iron storage, increasing quickly within 10 days following the treatment and decreasing after 6 months. This effect could be explained by the fact that the hemoglobin and ferritin levels are not reciprocally linear. Hemoglobin and ferritin levels post-treatment reflect erythropoietic recovery on the one hand, followed by a reactive decrease in ferritin due to feedback at the mRNA level on the other [25].

Iron sucrose administration was found to be a safe treatment with few, transient and reversible side effects, even in small children. Although iron overload was detected only in three patients, this suggests that an individual iron clearance should be determined and an individual protocol must be established for every child. We cannot explain why these particular patients manifested iron overload early in the course of treatment. Although the number of patients described in this study is relatively small, our data suggest that intravenous iron therapy should be considered in cases where oral administration has failed. Further research involving a larger population is needed to determine the safety and efficacy of intravenous iron therapy in children.

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