

Maintenance Intravenous Iron Sucrose Therapy in Children Under Regular Hemodialysis

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ABSTRACT

Background: In pediatric patients under regular hemodialysis, iron supplementation is essential for optimal response to erythropoietin therapy. Oral iron supplements may be insufficient to maintain total body iron stores in children under regular hemodialysis, and intravenous (IV) iron supplement might be an effective alternative but with variable safety of different preparations.

Objectives: To evaluate the effects of maintenance IV iron sucrose versus oral iron gluconate on iron indices and hematological profile in pediatric hemodialysis patients and reporting the safety of both preparations.

Methods: A cross over study was made on 16 children under regular hemodialysis (12 males and 4 females with median age 11 years) who had initial adequate iron stores as evidenced by serum transferrin saturation $\geq 20\%$ and/or serum ferritin ≥ 100 ng/ml. They were maintained on oral iron gluconate in a dose of 3 mg/kg/daily and erythropoietin alpha (EPO) therapy in a dose of 50 IU/kg/IV 3 times weekly for 3 months. Then a shift from oral iron to IV iron sucrose in a dose of 2 mg/kg/every 2 weeks in addition to EPO in the same previous dose and route was made for another 3 months.

Results: We reported significant changes between baseline follow-up investigations as follows: serum ferritin (median 345-505 ng/ml, $p = 0.002$), transferrin saturation (median 36.1-58.2%, $p = 0.001$), hemoglobin concentration (median 8.8-9.5 gm/dl, $p = 0.021$), and hematocrit (median 28.5-31.7%, $p = 0.002$).

Conclusions: We concluded that hemoglobin and hematocrit were significantly increased by (8%) and (11.2%) respectively in response to IV maintenance iron sucrose every 2 weeks. In addition, IV iron sucrose can be safely used as a maintenance preparation in children under regular hemodialysis to maintain adequate iron stores and response to EPO therapy with no or little increment in its doses.

INTRODUCTION

Effective erythropoiesis in children with chronic renal failure (CRF) under regular hemodialysis requires both erythropoietin (EPO) therapy and iron supplementation⁽¹⁾.

Erythropoietin increases the rate of erythropoiesis and mandates a greater amount of iron than that can be released from the reticuloendothelial system. A functional iron deficiency is likely to develop in all patients with chronic renal failure leading to limited erythropoiesis

although they might have initial adequate iron stores⁽²⁾.

The inability to absorb oral iron supplements in sufficient quantities to match the demand of heightened erythropoiesis constitutes the main mechanism of iron deficiency in patients with CRF treated with EPO⁽³⁾. In addition, continued blood loss in the hemodialysis circuits will further increase the demand of iron supplementation in patients under regular hemodialysis⁽⁴⁾.

Oral iron supplements may be insufficient to maintain total body iron stores in children with CRF under regular hemodialysis⁽⁵⁾, and intravenous (IV) iron supplement has been shown in adults to be an effective alternative^(6,7). However, few data exist on efficacy and safety of maintenance use of IV iron in pediatric patients⁽⁸⁾.

AIM OF THE WORK

The aim of this study was to evaluate the effects of maintenance IV iron sucrose versus oral iron gluconate supplementation on iron indices and the hematological profile in children with ESRD under regular hemodialysis who had initial adequate iron stores and below-target hemoglobin and hematocrit response to erythropoietin therapy. The safety and side effects of both iron preparations were reported.

PATIENTS AND METHODS

Patients

Sixteen patients with ESRD under regular hemodialysis were selected from the Hemodialysis Section of the Pediatric Nephrology Unit, Mansoura University Children's Hospital, Egypt; from October 2003 to March 2004.

Selection criteria

All patients had:

- I. Initial normal iron indices as evidenced by transferrin saturation (TSAT) $\geq 20\%$ and/or serum ferritin ≥ 100 ng/ml.
- II. Below-target hemoglobin < 11 gm/dl, and/or hematocrit $< 33\%$ although they had received EPO alpha prior to the study in a dose of 50 IU/kg/IV after

hemodialysis sessions 3 times weekly but they had not received iron supplementation.

Exclusion Criteria

Any patient with:

- I. Absolute iron deficiency as evidenced by TSAT $\leq 20\%$ and/or serum ferritin ≤ 100 ng/dl that mandated treatment with therapeutic intravenous iron sucrose doses after each hemodialysis session.
- II. Iron overload as evidenced by TSAT $\geq 50\%$ and/or serum ferritin ≥ 1000 ng/dl that mandated stoppage of any iron administration.
- III. Inflammatory states with positive C-reactive protein.

Methods

A cross over study was done by giving all patients treatment plan (A) for 3 months followed by treatment plan (B) for another 3 months as follow:

Treatment plan (A):

In the first 3 months of the study all patients received:

- I. Oral iron gluconate: 3 mg/kg/day in divided doses orally 1 hour pre-prandial or 2 hours post-prandial.
- II. EPO alpha: 50 IU/kg/IV/3 times weekly after each hemodialysis session.

Treatment plan (B):

During the second 3 months of the study all patients received:

- I. Iron sucrose: 2 mg/kg/every 2 weeks IV infusion in 20 cc normal saline (0.9%) over 15-30 minutes after hemodialysis the session with a maximum of 100 mg in each single dose.
- II. EPO alpha: 50 IU/kg/IV/3 times weekly after each hemodialysis session.

Precautions

Although the product labeling of iron sucrose does not indicate the need for a test dose before its administration, we performed a test dose by giving 0.25 mg/kg iron sucrose IV infusion in 50 cc normal saline (0.9%) over 15-30 minutes.

All patients were observed during the test dose and all other IV iron sucrose doses for symptoms and signs of any major complications as anaphylactic reactions.

Monitoring

Both iron indices and hematological profile were reported after each of plan A and plan B treatments. These included serum iron detected by the colorimetric method, serum ferritin detected by ELISA, total iron binding capacity (TIBC) detected by the colorimetric method, and serum transferrin saturation (TSAT) calculated as $TSAT = \text{serum iron} \times 100 / TIBC$. Hemoglobin and hematocrit were measured by Cell-DYN 3700 Coulter Counter.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Science (SPSS) for windows version 10. Parameters are expressed in median and comparison between parameters after plan A and plan B treatments was done by using Wilcoxon Signed Ranks Test.

RESULTS

Sixteen children (12 males and 4 females) were enrolled in the study (Table 1). Their median age was 11 years. All of them were on regular hemodialysis of at

least 3.5 hours per session/ 3 times weekly for 6 months prior to the study and had appropriate parameters of the dialysis efficiency ($Kt/V \geq 1.2$). They had initial adequate iron stores and below-target hemoglobin and hematocrit levels that did not mandate iron administration in therapeutic doses nor blood transfusions. Any child with significant anemia or absolute iron deficiency was not included.

During the 6 months of the study, iron indices and hematological profile were done twice after the end of 3 months of plan A (oral iron gluconate) and at the end of plan B (intravenous iron sucrose) while maintaining all patients on the same EPO dose and route.

Satisfactory and adequate iron indices with improvement in hematological profile were reported during the study (Table 2). There was a significant increase in serum iron ($p = 0.002$), serum ferritin ($p = 0.026$), and TSAT ($p = 0.001$) after (IV) iron sucrose compared with oral iron gluconate. Hemoglobin and hematocrit were increased by (8%) and (11.2%) respectively after maintenance IV iron sucrose, and with the same fixed dose and route of EPO that was given to all patients all through the study period.

No major adverse effects were reported with either forms of iron supplementation (Table 3) apart from the risk of iron overload that was reported in 3 cases only after IV iron sucrose as evidenced by $TSAT \geq 50\%$ and/or serum ferritin ≥ 800 ng/ml.

Table 1: Clinical and laboratory characteristics of the patients prior to study.

Clinical and Laboratory Characteristics of Patients (No. = 16)	Parameters*
Age	11 years
Duration of hemodialysis prior to study	6 months
Kt/v	1.2
Serum Iron	75 mg/dl
TIBC	300%
TSAT	25%
Serum ferritin	257 ng/ml
Hemoglobin	8.4 g/dl
Hematocrit	27.4%

* Parameters are expressed as median.

Table 2: Comparison between iron indices and hematological profiles after oral iron (plan A), and IV iron sucrose (plan B) treatments.

Studied Parameter*	After plan A (No. =16)	After plan B (No. =16)	p	Change**
S. Iron (mg/dl)	77	114	0.002	▲ 48.1%
TIBC (%)	242.5	206.5	0.093	▼ 14.8%
TSAT (%)	36.1	58.2	0.001	▲ 61.2%
S. Ferritin (ng/ml)	345	505	0.026	▲ 46.4%
Hemoglobin (g/dl)	8.8	9.5	0.021	▲ 8%
Hematocrit (%)	28.5	31.7	0.002	▲ 11.2%

* Parameters are expressed in median

** % increase or decrease

Table 3: Main reported side effects (SE) after oral iron (plan A) and with IV iron sucrose (plan B) administration

Plan A		Plan B	
SE	No. (%)	SE	No. (%)
Constipation	14 (87.5%)	Pruritis	4 (25%)
Nausea	10 (62.5%)	Headache	3 (18.75%)
Vomiting	2 (12.5%)	Iron overload	3 (18.75%)
		Abdominal pain	1 (6.25%)
		Muscle cramps	1 (6.25%)
		Hypotension	1 (6.25%)

DISCUSSION

Ongoing hemodialysis will decrease iron stores with frequent blood loss from repeated sampling, retained blood in dialyzers, tubing sets, and vascular accidents⁽⁹⁾. It was reported that the cumulative annual iron losses in pediatric hemodialysis patients approximate 1.6 g/1.73 m² surface area. Thus, approximately about 400-500 mg of supplemental iron will be needed every 3 months to replace losses and maintain iron stores⁽¹⁰⁾.

The clinical practice guidelines of the National Kidney Foundation-Dialysis Outcomes Quality Initiatives (NKF-DOQI) support the implementation of IV iron regimens in hemodialysis adult patients⁽¹⁾. A number of iron preparations are being used for IV parenteral iron supplementation in chronic renal failure such as iron dextran, iron gluconate and iron sucrose⁽¹¹⁾. However, few data exist on efficacy and safety of maintenance use of IV iron preparations in pediatric patients⁽⁸⁾.

Clinical studies are trying to define the role of chronic IV iron therapy and to establish appropriate dosing schedules for different IV iron preparations. Intravenous iron dextran was reported to be an effective alternative to oral iron in pediatric hemodialysis patients⁽¹²⁾, but can be associated with life threatening conditions as fatal anaphylactic allergic reactions⁽¹³⁾.

We evaluated the effects of maintenance IV iron sucrose versus oral iron gluconate supplementations on iron indices and the hematological profile in children with ESRD under regular hemodialysis who had initial adequate iron stores and below-target response to erythropoietin therapy

although they had efficient hemodialysis ($Kt/v \geq 1.2$).

In our study, although all patients had initial normal iron indices, both TSAT and serum ferritin increased significantly ($p = 0.001$, and 0.026 respectively) after giving maintenance iron doses as the sucrose form by IV route every 2 weeks compared with daily oral gluconate form. In addition, hemoglobin and hematocrit increased significantly after the use of maintenance IV iron sucrose by (8%) and (11.2%) respectively compared with oral iron gluconate and with the same EPO dose and route all through the study. However, target hemoglobin level of $\geq 11-12$ g/dl and hematocrit of $\geq 33\%$ were not attained during nor at the end of the study. This might signify that IV iron could enable a lesser increment of EPO doses than with oral iron to obtain target hematological profile.

These results could be explained by the fact that the absorptive capacity of oral iron from the uremic gut is reduced and may be also limited by the concomitant administration of H₂ receptor blockers⁽¹⁴⁾, and calcium containing phosphate binders⁽¹⁵⁾. Furthermore, poor patient compliance to oral iron regimens with inconvenient dose scheduling (1 hour pre-prandial, 2 hours postprandial), or side effects as gastrointestinal irritation, and constipation might be additional factors⁽¹⁾.

The safety profile of IV iron sucrose was satisfactory in our study as no one experienced any major side effects like fatal anaphylactic reactions that were reported with iron dextran preparations in other trials⁽¹¹⁾. Although the risk of iron overload

is difficult to determine and little information in the literature clearly establishes the safe upper limit of serum ferritin and TSAT⁽³⁾, three patients only in our study attained very high TSAT of $\geq 50\%$ and/or serum ferritin of ≥ 800 ng/ml. However, our children experienced better tolerability and compliance to IV iron sucrose than with oral iron as the latter was associated with gastrointestinal irritation and constipation in the majority of studied patients.

In agreement with our results, Morgan et al.⁽¹⁶⁾ reported that IV iron sucrose in maintenance doses every one week is safe and efficient in maintaining satisfactory iron indices and the hematological profile as well as decreasing doses and cost of EPO in pediatric hemodialysis patients.

In conclusion, we have demonstrated that effective erythropoiesis in children under regular hemodialysis requires both erythropoietin therapy and iron supplementation even if their initial iron stores are satisfactory. Maintenance IV iron sucrose increases hemoglobin and hematocrit better than oral iron gluconate. The benefits of IV iron sucrose are expected to exceed its adverse effects. Although target hemoglobin and hematocrit could not be attained in our study, small increments in EPO dose in conjunction with IV maintenance iron sucrose every 2 weeks are recommended to achieve a satisfactory hematological profile and maintain adequate iron stores in children undergoing hemodialysis.

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