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Maintenance Intravenous Iron Sucrose Therapy in Children Under Regular Hemodialysis

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This study aimed to evaluate the effects of maintenance IV iron sucrose vs oral iron gluconate on iron indices and hematological profile in pediatric hemodialysis patients. Twenty four children under regular hemodialysis (13 males and 11 females with median age 11 years) were enrolled in this study and had initial adequate iron stores and were maintained on oral iron gluconate daily and erythropoietin alpha (EPO) weekly for 3 months prior to study. They were randomly subdivided into two groups. Group A included 12 patients (8 males and 4 females with median age 10 years) and they continued to receive oral iron gluconate daily and EPO alpha and group B included 12 patients (5 males and 7 females with median age 12 years) who received intravenous iron sucrose every 2 weeks and EPO alpha on same dose of group A for a study period of 3 months. There were significant increase in serum iron ($p = 0.002$), serum ferritin ($p = 0.026$) and transferrin saturation ($p = 0.001$) in (IV) iron sucrose group than with oral iron gluconate group. In addition, hemoglobin and hematocrite were increased by 8 and 11.2%, respectively on group B. Iron overload was reported in two patients only of group B (16.7%). We concluded that IV iron sucrose is effective and safe preparation to be used in iron replete children under regular hemodialysis to maintain adequate iron stores and to ensure optimum response to EPO therapy.

Key words: Chronic renal failure, anemia, iron therapy

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INTRODUCTION

Effective erythropoiesis in children with Chronic Renal Failure (CRF) under regular hemodialysis requires both erythropoietin (EPO) therapy and iron supplementation. Iron administration plays a central role in enhancing anemia responsiveness to EPO (Kalantar-Zadeh *et al*., 1995).

Erythropoietin increases the rate of erythropoiesis and mandates greater amount of iron than that can be released from 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 (Khosh *et al*., 2001).

The vast majority of CRF patients seem to be iron deficient, because of multiple interferences with all phases of iron metabolism: Reduced iron intake, reduced gastro-intestinal iron absorption, gastro-intestinal bleeding, urinary loss of iron in patients with heavy proteinuria and reduced hematopoietic utilization of the orally administered iron (Mircescu *et al*., 2006).

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 (Besarab *et al*., 1999). In addition, continued blood loss in the hemodialysis circuits will further increase the demand of iron supplementation in patients under regular hemodialysis (Fishbane *et al*., 1995).

Oral iron supplements may be insufficient to maintain total body iron stores in children with CRF under regular hemodialysis (Greenbaum, 2005) and intravenous (IV) iron supplement has been shown in adults to be an effective alternative (Sunder-Plassmann and Horl, 1995; Fishbane *et al*., 1999). However, few data exist on efficacy and safety of maintenance use of IV iron in pediatric patients (Warady *et al*., 2006).

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

MATERIALS AND METHODS

Twenty four patients with CRF under regular hemodialysis were selected from Hemodialysis Section of Pediatric Nephrology Unit, Mansoura University Children's Hospital, Egypt during the period between December, 2004 and March, 2005. All patients enrolled in this study were on regular hemodialysis of at least 3.5 h per session/3 times weekly for 3 months prior to study and had appropriate parameters of dialysis efficiency (Kt/V≥1.2). They had initial adequate iron stores as evidenced by transferrin saturation (TSAT) ≥20% and/or serum ferritin≥100 ng mL^{-1} according to National Kidney Foundation Clinical Practice Guidelines (NKF-K/DOQI, 2001). All patients and/or their parents gave written consent to be included in this study.

All patients had below target hemoglobin (<11 g dL^{-1}) and/or hematocrite (<33%) but did not receive iron administration in therapeutic doses nor blood transfusions (Table 1). They were receiving oral iron gluconate at dose 3 mg kg^{-1} day in divided doses orally in addition to EPO alpha at dose 50 IU/kg/IV/3 times weekly after each hemodialysis session for at least 3 months prior to study. All children and/or their parents gave informed written consent to participate in our study and they were randomly subdivided into two groups:

Group A: It included 12 patients (8 males and 4 females with median age 10 years). In this group of patients we continued to give them through out the 3 months of study:

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

Group B: It included 12 patients (5 males and 7 females with median age 12 years). They received for the 3 months of study:

- Iron sucrose: 2 mg kg^{-1} every 2 weeks IV infusion in 20 cc normal saline (0.9%) over 15-30 min after hemodialysis session with maximum of 100 mg in each single dose.

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

Clinical and laboratory characteristics of patients (No. = 24)	Median parameters
Age	11 years
Duration of hemodialysis	3 months
Kt/v*	1.2
Serum Iron	75 mg dL^{-1}
TIBC*	300%
TSAT*	25%
Serum ferritin	257 ng mL^{-1}
Hemoglobin	8.4 g dL^{-1}
Hematocrite	27.4%

*TIBC: Total iron binding capacity, *TSAT: Transferrin saturation, *Kt/v: a measure of dialysis efficiency where k: dialyzer clearance, t: time of dialysis session, v: volume of urea distribution

- EPO alpha: 50 IU/kg/IV/3 times weekly after each hemodialysis session.

Precautions: We performed a test dose by giving 0.25 mg kg^{-1} iron sucrose IV infusion in 50 cc normal saline (0.9%) over 15-30 min. All patients were observed during test dose and all other IV iron sucrose doses for symptoms and signs of any major complications as anaphylactic reaction.

Exclusion criteria: Any patient with any of the following was excluded from the study:

- Absolute iron deficiency as evidenced by TSAT ≤20% and/ or serum ferritin ≤100 g dL^{-1} that mandated treatment with therapeutic intravenous iron sucrose doses after each hemodialysis session.
- Iron overload as evidenced by TSAT ≥50% and/or serum ferritin ≥ 800 ng dL^{-1} that mandated stoppage of any iron administration.
- Inflammatory states with positive C-reactive protein.

Laboratory monitoring: Iron indices and hematological profile were reported. Serum iron detected by colorimetric method (Randox). Serum ferritin detected by solid phase direct sandwich ELISA method. Total Iron Binding Capacity (TIBC) detected by colorimetric method (Randox) and serum transferrin saturation (TSAT) calculated, as TSAT equals serum iron X100/TIBC. Hemoglobin and hematocrite were detected by automated cell Counter, Cell-DYN 3700.

Statistical analysis: Data were analyzed using Statistical Package for the Social Science (SPSS, 1999) for windows version 10. Parameters are expressed in median and analysis of difference for quantitative variables was done by Mann Whitney U-Willcoxon Ranks Sum W. Test.

RESULTS

Satisfactory and adequate iron indices with improvement in hematological profile were reported during the study (Table 2). There was significant increase in serum iron ($p = 0.002$), serum ferritin ($p = 0.026$) and TSAT ($p = 0.001$) after (IV) iron sucrose than with oral iron gluconate. Hemoglobin and hematocrite 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 2 cases only after IV iron sucrose as evidenced by TSAT≥50% and/or serum ferritin≥800 ng mL^{-1}.

Table 2: Comparison between iron indices and hematological profiles with oral iron gluconate (group A) and IV iron sucrose (group B)

Studied parameter*	Group A (No = 12)	Group B (No = 12)	p-value	% of change from base line values
S. Iron (mg dL^{-1})	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^{-1})	345	505	0.026	↑ 46.4%
Hemoglobin (g dL^{-1})	8.8	9.5	0.021	↑ 8%
Hematocrite (%)	28.5	31.7	0.002	↑ 11.2%

TIBC: Total iron binding capacity, TSAT: Transferrin saturation *Parameters are expressed in median ↑: trend increase from baseline value, ↓: trend decrease from baseline value

Table 3: Main reported Side Effects (SE) after oral iron (group A) and with IV iron sucrose (group B)

Group A (No. =12)		Group B (No.=12)	
SE	No. (%)	SE	No. (%)
Constipation	10 (83.3%)	Pruritis	4 (33.3%)
Nausea	9 (75%)	Headache	3 (25%)
Vomiting	2 (16.7%)	Iron overload	2 (16.7%)
		Abdominal pain	1 (8.3%)
		Muscle cramps	1 (8.3%)
		Hypotension	1 (8.3%)

DISCUSSION

Ongoing hemodialysis decrease iron stores with frequent blood loss from repeated sampling, retained blood in dialyzers, tubing sets and vascular accidents (Flores *et al*., 1999). It was reported that the cumulative annual iron losses in pediatric hemodialysis patients approximate 1.6 g/1.73 m^2 surface area. For so, approximately about 400-500 mg of supplemental iron will be needed every 3 months to replace losses and maintain iron stores (MacDougall, 1999).

The clinical practice guidelines of the National Kidney Foundation-Dialysis Outcomes Quality Initiatives (NKF-DOQI) support the implementation of provocative IV iron regimens in hemodialysis adult patients (IV-National Kidney Foundation, 2001). 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 (Chertow *et al*., 2004). However, few data exist on efficacy and safety of maintenance use of IV iron preparations in pediatric patients (Sakiewiez and Paganini, 1998).

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 effective alternative to oral iron in pediatric hemodialysis patients

(Ruiz-Jaramillo *et al*., 2004), but can be associated with life threatening conditions as fatal anaphylactic allergic reaction (Greenbaum *et al*., 2000).

We evaluated the effects of maintenance IV iron sucrose versus oral iron gluconate supplementations on iron indices and hematological profile in children with CRF and 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 this 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 sucrose form by IV route every 2 weeks at dose 2 mg kg^{-1} than with oral daily 3 mg kg^{-1} of iron gluconate form. In addition, hemoglobin and hematocrite increased significantly after the use of maintenance IV iron sucrose by 8 and 11.2%, respectively than after oral iron gluconate and with the same EPO dose and route all through the study. However, target hemoglobin level of ≥11-12 g dL^{-1} and hematocrite of≥33% were not attained during and at the end of the study. This might signify that IV iron could enable a little increment of EPO doses than with oral iron to obtain target hematological profile.

These results could be explained by the fact that absorptive capacity of oral iron from uremic gut is reduced and may be also limited by the concomitant administration of H_2 receptor blockers (Conrad, 1987) and calcium containing phosphate binders (Whiting, 1995). Furthermore, poor patient compliance to oral iron regimens with inconvenient dose scheduling (1 h pre-prandial, 2 h postprandial), or side effects as gastrointestinal irritation and constipation might be additional factors (IV-National Kidney Foundation, 2001).

Safety profile of IV iron sucrose was satisfactory in our study as no one experienced any major side effects like fatal anaphylactic reaction that was reported with iron dextran preparation in other trials (Chertow *et al*., 2004). Although the risk of iron overload is difficult to determine and little information in the literature clearly establish the safe upper limit of serum ferritin and TSAT (Besarab *et al*., 1999), two patients only in our study attained very high TSAT of ≥50% and/or serum ferritin of ≥800 ng mL^{-1}. 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.

Few studies reported the effects of maintenance IV iron sucrose for children who are not iron depleted. In agreement with our study, Morgan *et al*. (2001) retrospectively studied 2 mg kg^{-1} $week^{-1}$ maintenance IV iron sucrose, which is same dose we gave to our patients but at weekly basis and they reported that this regimen is safe and efficient in maintaining satisfactory iron indices and hematological profile as well as decreasing doses and cost of EPO in pediatric hemodialysis patients. However, Leijn *et al*. (2004) studied the effects of lower and frequent doses of maintenance IV iron sucrose therapy by giving 0.3 mg kg^{-1}/dialysis session 3 times per week and founded that iron status remained at a constant level for several weeks and suggested that doses higher can cause iron overload.

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 hematocrite better than oral iron gluconate. The benefits of IV iron sucrose are expected to exceed its adverse effects. Although nearly target hemoglobin and hematocrite could not be attained in our study, a little increment 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 with ongoing hemodialysis.

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