

## Intravenous Iron Supplementation in Korean Children on Chronic Dialysis

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### = Abstract =

**Purpose:** Limited information is available on experiences of intravenous iron treatment in children. In this study, iron sucrose was administered intravenously to determine its effect, the factors predicting outcome, and safety in children on chronic dialysis.

**Methods:** Twenty-one children whose serum ferritin levels were less than 100 ng/mL or transferrin saturations (TSAT) were less than 20% were enrolled. In 12 children on peritoneal dialysis (PD), the drug was infused intravenously as 200 mg/m<sup>2</sup> (≤200 mg) at week 0, 2, 4, and 6. In 9 children on hemodialysis (HD), it was given intravenously as 8 weekly doses of 3 mg/kg (≤100 mg) through week 0-7.

**Results:** After treatment, serum ferritin levels increased significantly in both groups, and TSAT rose significantly in PD group. However, hemoglobin level did not rise significantly in both groups. Children with baseline hemoglobin less than 10 g/dL or baseline TSAT less than 20% showed significantly higher rise of hemoglobin after intravenous iron treatment. To the contrary, those with higher baseline hemoglobin and TSAT levels displayed higher rise in serum ferritin after the treatment. Although no serious adverse event occurred, TSAT levels exceeding 50% were noted in 6 patients in PD group.

**Conclusion:** This suggests that 3 mg/kg/week of intravenous iron sucrose can be used safely in children on chronic HD, but 200 mg/m<sup>2</sup> every other week may incur excessive TSAT level in some patients on chronic PD. (*J Korean Soc Pediatr Nephrol* 2009; 13: - )

**Key Words:** Intravenous, iron sucrose, Peritoneal dialysis, Hemodialysis, Children, Factors predicting outcome, Safety, Dosage

### Introduction

Anemia is a common manifestation of end stage

renal disease (ESRD) and results in a variety of complications, e.g., cardiovascular, neuromuscular, energy, and mental dysfunctions [1-3]. Anemia of ESRD is usually associated with erythropoietin deficiency [1], and is managed by replacing erythropoietin with recombinant protein [4-6]. However, as substitution with recombinant human erythropoietin (rHuEpo) depletes body iron storage, concurrent administration of iron is required

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in most patients [1, 7, 8], but supplementation of iron via the oral route is often ineffective or inadequate in patients on hemodialysis (HD) [1]. In addition, gastrointestinal discomfort can have some patients intolerant to oral iron. Therefore, parenteral administration of iron is recommended to achieve adequate iron stores in ESRD patients on HD [1, 9]. In children on HD, 1-7 mg/kg/week of intravenous iron has been reported to be effective in repletion of iron deficiency or in maintaining iron store [10-15].

On the other hand, discomfort and inconvenience of intravenous infusions preclude the widespread use of intravenous iron in patients on peritoneal dialysis (PD) [9]. Thus, the oral route remains the main way of iron supplementation in patients on PD, which may expose these patients to the risk of iron deficiency despite the administration of maximal oral iron dosages [16-18]. Moreover, no definite dosage guideline has been available for intravenous iron treatment in children on chronic PD.

The purpose of this study is to ascertain the efficacy, factors predicting the outcome, and the safety of intravenous iron sucrose in children on chronic dialysis.

## Material and Methods

### 1. Patients and treatment

A prospective, open-labeled, single group clinical trial was conducted to investigate the efficacy, factors predicting outcome, and safety of intravenous iron sucrose in iron-deficient children on chronic dialysis. Children's ages ranged from 4 to 18 years, and all were on oral iron and paren-

teral rHuEpo therapy. Consent was obtained from parents or legal guardians before enrollment in this study.

Inclusion criteria included; (1) a ferritin level of <100 ng/mL or (2) a transferrin saturation (TSAT) of <20% despite the usual dosage (elementary iron 2-3 mg/kg/day) of oral iron supplement. Exclusion criteria included active infections, inflammatory conditions, transfusions or major surgery during the previous 1 month, and iron overload (defined as TSAT >50% or serum ferritin exceeding 500 ng/mL).

The study drug, iron hydroxide sucrose (Venoferrum<sup>®</sup>, Choongwae Pharma Corp., Korea; Venofer<sup>®</sup>, Vifor Int., Switzerland) was infused after diluting to a concentration of 1 mg/mL with normal saline. It was infused intravenously as 200 mg/m<sup>2</sup> (≤200 mg) over 1 hour at week 0, 2, 4, and 6 in children on chronic PD, and as 8 weekly doses of 3 mg/kg (≤100 mg) over 30 minutes through week 0-7 in children on chronic HD. Oral iron preparations were discontinued from the 1st intravenous iron dose, and when there is no evidence of iron overload, resumed at 4 weeks after cessation of intravenous treatment. The rHuEpo was administered subcutaneously in PD group and by intravenous route in HD group with dosage adjustment targeting hemoglobin levels to 10.0-11.0 g/dL according to the recommendation by the Korean Health Insurance Association.

### 2. Evaluation of the efficacy and factors predicting the outcome

To evaluate efficacy, hemoglobin, serum ferritin levels, TSAT, and reticulocyte counts were obtained at baseline just before the 1st administration

(week 0), and at week 4, 8, 12, and 16 after the 1st dose of intravenous iron sucrose.

To identify the factors predicting outcome of the intravenous iron treatment, we calculated the differences of hemoglobin, serum ferritin, and TSAT values (hemoglobin, ferritin, TSAT) at week 4, 8, and 12 from the respective baseline values, and compared them between groups of different dialysis modalities, baseline hemoglobin, ferritin, and TSAT levels. Mean dosages of rHuEpo used in the study period were also compared between the groups.

### 3. Safety

Safety was assessed by monitoring adverse events including paying special attention to anaphylactic reactions, non-anaphylactic allergic reactions, and hypotensive episodes. Blood pressure, heart rate, respiratory rate, and axillary temperature were measured prior to administration, and repeated at 30 and 60 minutes after administration. In addition, these were repeated and adverse events were evaluated at every hospital visits till week 16.

### 4. Statistical methods

All values were expressed as mean±standard deviation. Mann-Whitney U tests were conducted to compare the values at week 4, 8, and 12 with the respective baseline values as well as the values between the groups. Analyses of significances were conducted at  $P=0.05$  (two-tailed).

## Results

### 1. Baseline demographics and clinical characteristics

Twenty-one patients (12 on chronic PD and 9 on chronic HD) completed the study. Patient's demographic and baseline clinical characteristics are presented in Table 1. In all patients enrolled, baseline ferritin levels were less than 100 ng/mL, while baseline TSAT levels were less than 20% (absolute iron deficiency) in 6 (4 in the HD group, 2 in the PD group) patients. Baseline hemoglobin levels tend to be lower in the HD group, but the difference was not statistically significant ( $9.3 \pm 1.5$  g/dL in the HD group vs.  $10.7 \pm 1.5$  g/dL in the PD group,  $P=0.069$ ). Mean baseline rHuEpo dose was significantly higher in the HD group than in the PD group ( $362 \pm 121$  IU/kg/week in the HD group vs.  $182 \pm 99$  IU/kg/week in the PD group,  $P=0.003$ ). No other baseline hematologic

**Table 1.** Demographic and Clinical Characteristics of the Patients

Dialysis Modality	Hemodialysis	Peritoneal Dialysis
Number of patients	9	12
Age (median, years)	8.8 (2.1-11.7)	11.0 (4.1-17.2)
Sex (Male : Female)	6:3	4:8
Months on dialysis	$32.3 \pm 19.2$	$23.6 \pm 28.0$
Kt/V, weekly (baseline)	$2.2 \pm 0.5$	$2.2 \pm 0.5$
Causes of ESRD		
Glomerulonephritis	2	4
Reflux nephropathy	1	3
Cystic renal disease	3	0
Systemic disease	0	3
Others	3	2

Abbreviation : ESRD, end-stage renal disease

data or iron indices showed any significant difference between the two groups (Table 2).

## 2. Efficacy and factors predicting the outcome

Hematologic parameters and iron indices at baseline, week 4, 8, and 12 are presented in Table 2. Increments in hemoglobin, ferritin, and TSAT values at week 4, 8, and 12 from the baseline ( $\Delta$  hemoglobin,  $\Delta$ ferritin,  $\Delta$ TSAT) are presented in Table 3. The mean dosages of rHuEpo and baseline laboratory values between HD and PD group are compared in Table 3.

**Hemoglobin response:** In children in both dialysis modalities, hemoglobin did not increase significantly after treatment of intravenous iron sucrose, though in HD group, the mean hemoglobin levels revealed the tendency of increments with the intravenous iron treatment. However, increments in hemoglobin at week 4, 8, and 12 from the baseline were significantly higher in children with baseline hemoglobin <10 g/dL or baseline TSAT <20%.

**Iron Indices:** Compared with baseline values,

serum ferritin levels increased significantly at week 4 and 8 in HD group and at week 4, 8, and 12 in PD group (Table 2). All patients in the PD group and 89% of patients in the HD group revealed serum ferritin level >100 ng/mL at week 8. Seventy percent of the PD group and 66% of the HD group maintained serum ferritin level >100 ng/mL till week 16 and this findings revealed that a target ferritin level maintained at 10 and 9 weeks after the last administration of intravenous iron dose in PD and HD group respectively. Changes in serum ferritin at week 4 from the baseline level were significantly higher in children with baseline hemoglobin  $\geq$ 10 g/dL or baseline TSAT  $\geq$ 20% g/dL. Increment in serum ferritin at week 12 from the baseline was significantly higher in children on PD.

TSAT increased significantly from a baseline mean value of  $27.4 \pm 10.2\%$  to  $45.7 \pm 23.2\%$  at week 8 in the PD group ( $P=0.006$ ). However, TSAT did not rise significantly in the HD group. TSAT levels were over 20% in all PD group and 56% of the HD group at week 8. Seventy-four percent of PD group and 37% of HD group maintained the levels higher than 20% till week 12 which is 6

**Table 2.** Hematologic and Iron Indices before and after Intravenous Iron Treatment

	HD Group (n=9)				PD Group (n=12)			
	Baseline	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12
Hgb (g/dL)	9.3±1.5	9.8±1.2	10.3±1.3	9.9±1.3	10.7±1.5	10.6±1.7	10.5±2.2	10.0±1.3
Ferritin (ng/mL)	51±34	151±108*	248±135*	136±123	32±25	209±104*	361±188*	337±186*
TSAT (%)	23.2±11.1	25.4±8.0	26.1±11.3	24.3±14.0	27.4±10.2	38.4±23.3	45.7±23.2*	42.9±20.9
Reticulocyte (%)	1.3±0.7	1.2±0.4	1.3±0.7	1.2±0.5	1.5±0.9	1.7±0.7	1.6±1.0	2.0±1.2
rHuEpo dose (IU/kg/wk)	362±121	362±119	365±117	309±99	182±99	175±101	165±109	165±105

Weeks since the 1st dose of i.v. iron sucrose infusion.

\* $P<0.05$  compared with the baseline value.

Abbreviations : Hgb, hemoglobin; TSAT, transferrin saturation; rHuEpo, recombinant human erythropoietin

**Table 3.** Changes in Hemoglobin, Ferritin, and Transferrin Saturation, and the Mean Dosage of Recombinant Human Erythropoietin Dosage used in the Study Period between Groups of Patients Divided by Dialysis Modality and Baseline Laboratory Values

Group	n	Hgb (g/dL)			Ferritin (ng/mL)			TSAT (%)			Mean rHuEpo Dose IU/kg/wk
		Week 4	Week 8	Week 12	Week 4	Week 8	Week 12	Week 4	Week 8	Week 12	
Dialysis Modality											
HD	9	0.48±1.41	0.98±1.08	0.62±1.44	99±92	197±135	87±119	2.2±11.5	2.9±15.5	0.9±15.8	345±93
PD	12	0.01±1.81	-0.11±2.43	-0.73±2.20	176±94	329±184	305±202	10.9±19.2	18.3±21.3	15.7±21.4	171±102
<i>P</i>		0.434	0.145	0.220	0.057	0.177	0.027	0.849	0.177	0.155	0.002
Baseline Hgb											
<10 g/dL	10	0.99±1.41	1.18±1.22	1.14±0.83	89±83	264±202	146±210	0.5±10.9	4.8±16.3	3.6±19.0	291±123
≥10 g/dL	11	-0.49±1.54	-0.39±2.33	-1.45±1.97	184±92	280±155	283±161	12.2±18.6	18.0±21.9	16.0±20.3	208±130
<i>P</i>		0.038	0.018	0.002	0.014	0.888	0.097	0.239	0.205	0.183	0.130
Baseline Ferritin											
< 50 ng/mL	14	0.48±1.65	0.40±2.19	-0.25±2.14	137±99	296±182	258±192	9.5±19.5	14.4±23.3	12.3±22.4	208±107
≥50 ng/mL	7	-0.32±1.57	0.27±1.74	0.26±1.61	150±104	225±161	69±157	2.3±7.2	6.3±10.8	0.8±9.2	325±144
<i>P</i>		0.279	0.823	0.930	0.781	0.765	0.058	0.362	0.456	0.218	0.068
Baseline TSAT											
<20%	6	1.80±1.04	1.86±0.73	1.21±0.87	74±40	302±116	193±257	6.1±4.5	13.2±11.2	11.6±17.4	274±116
≥20%	15	-0.42±1.38	-0.24±2.05	-0.69±2.04	171±103	260±195	208±173	7.4±19.6	11.1±23.1	7.9±21.8	239±139
<i>P</i>		0.004	0.005	0.043	0.039	0.350	0.615	0.564	0.392	0.640	0.509

sAbbreviations : Hgb, hemoglobin; TSAT, transferrin saturation; rHuEpo, recombinant human erythropoietin

weeks and 5 weeks after the last administration of intravenous iron dose in PD and HD group respectively. Increment of TSAT from the baseline after the intravenous iron treatment was not different between groups of different dialysis modalities or baseline laboratory values.

**Anemia Intervention:** The mean rHuEpo dosage of PD group was less than that of HD group (Table 2,  $P=0.002$ ). Though mean rHuEpo dose did not change significantly during the study period, it was reduced in 2 patients of HD group and in 3 patients of PD group.

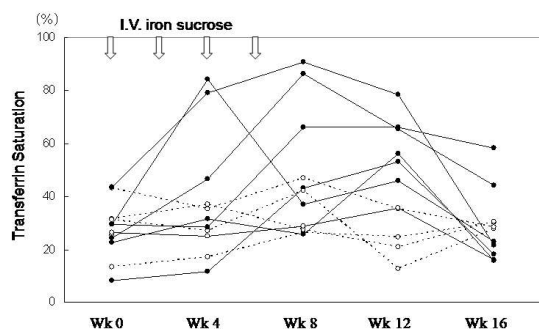
### 3. Safety

No serious adverse event requiring discontinuation of the intravenous iron treatment occurred. However, two children in the PD group complained of episodes of a chilling sense and mild fever during infusion which subsequently disappeared

spontaneously. No anaphylactic reaction or hypotension occurred during this study. In addition, no active infection, inflammatory condition, or abnormality by liver function testing was observed during or after iron sucrose treatment.

### 4. Iron overload

No patients registered a serum ferritin value >800 ng/mL during or after treatment. However, 6 patients (50%) in the PD group showed TSAT levels higher than 50% during or after treatment (Fig. 1). TSAT levels remained high until week 12 in 5 patients and even till week 16 (10 weeks after the last intravenous dose) in one patient. Although two of these 6 patients with high TSAT revealed a relatively high serum ferritin level (605 and 674 ng/mL), the ferritin levels of the other 4 patients were less than 500 ng/mL.



**Fig. 1.** Transferrin saturation levels during and after intravenous iron treatment in children on peritoneal dialysis. Six patients (closed circles) showed transferrin saturation levels higher than 50% during or after intravenous iron sucrose treatment (vertical arrows); high levels were maintained until week 12 in 5 patients and until week 16 in a patient.

## Discussion

Adequate iron levels are important for the management of iron-deficiency anemia. However, the precise determination of iron status in ESRD is difficult because of common co-morbid conditions that can affect body iron store indices [19, 20]. Despite these limitations, TSAT and serum ferritin remain the cornerstones of iron status assessment [1, 18, 19]. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practical Guidelines recommend that hemoglobin should be maintained at 11-13 g/dL with sufficient iron supplementation to maintain TSAT >20% and serum ferritin >100 ng/mL [1]. Given the prevalence of iron deficiency in ESRD patients, and the sensitivity and specificity of TSAT and serum ferritin in terms of iron deficiency detection, the likelihood of iron deficiency is sufficiently high when TSAT is <20% and serum ferritin is <100 ng/mL [1].

There was a discrepancy between incidence of

hypoferritinemia and low TSAT before intravenous iron treatment in this study. Though all enrolled patients showed serum ferritin <100 ng/mL, only 4 children in HD group and 2 in PD group fulfilled the criteria for absolute iron deficiency of chronic kidney disease by NKF-K/DOQI (TSAT level <20%). This means that storage iron was depleted in all but the mobilized iron was not exhausted in many patients. We suppose that these characteristics of the patients can explain why intravenous iron supplementation raised serum ferritin levels without further increment of TSAT in this study. It is also assumed that some increments of the mean TSAT in PD group may be related with the relatively higher baseline TSAT levels in the group ( $27.4 \pm 10.2\%$  in PD group vs.  $23.2 \pm 11.1\%$  in HD group). This finding may suggest that the dose of intravenous iron should be reduced in the patients who had a normal TSAT value and a very low serum ferritin value.

Three intravenous iron preparations are currently approved for use, i.e., iron dextran, sodium ferric gluconate complex in sucrose, and iron sucrose. Serious type I allergic reactions may occur more often with iron dextran administration and have been associated with fatal and life-threatening outcomes [21]. Recently, iron sucrose has been reported to carry the lowest risk of a hypersensitivity reaction [21], and to be an effective and safe supplement for iron deficiency in ESRD [10-14, 16-18, 22-27]. Safety data in pediatric patients is limited. In previous studies on iron dextran use in pediatric patients, one of the 28 patients developed an allergic reaction requiring termination of intravenous iron treatment [23, 24]. However, previous pediatric experience with iron sucrose

showed that no patient among 106 developed an allergic reaction requiring discontinuance of intravenous iron treatment [13,28]. Our study confirmed that the use of iron sucrose with the dosage of 200 mg/m<sup>2</sup>/dose or 3 mg/kg/dose did not produce any serious adverse effects except a few self-limited episodes of chilling sense and mild fever.

In our study, the patients with higher baseline hemoglobin and TSAT levels displayed relatively higher rise in serum ferritin during or after the treatment. However, no patient showed a serum ferritin value >800 ng/mL during or after treatment. According to the NKF-K/DOQI Clinical Practical Guidelines, there is no evidence to recommend administration of intravenous iron if serum ferritin is  $\geq 500$  ng/mL [1]. They also recommended that in patients in whom TSAT is  $\geq 50\%$  and/or serum ferritin is  $\geq 800$  ng/mL, intravenous iron should be withheld for up to 3 months [1]. Usually, the definition of an iron overload is that serum ferritin chronically remains over 1,000 ng/mL [29]. A study found that a ferritin level >600 ng/mL increases mortality among HD patients [30], and a recent observational study in adults showed that a serum ferritin level of 800 ng/mL was associated with the mortality in maintenance HD patients due to the confounding effects of malnutrition-inflammation-cachexia syndrome [31]. Though iron overload has been reported to increase the risk of bacterial infections [32-34], it should be noted that, because ferritin is an acute phase reactant, higher adverse events in hyperferritinemia are not always associated with iron overload but may be confounded by non-iron-related conditions [1, 19, 20, 31].

Our results failed to prove that intravenous iron

sucrose raise hemoglobin significantly, while it increases serum ferritin levels. In HD group, though statistical difference was not proven, as the mean hemoglobin levels revealed the tendency of increments with the intravenous iron treatment, we speculated that statistical insignificance might be derived from the small number of patients (n=9) in this group. However, in PD group, the hemoglobin levels did not show any tendency of increment. Instead, as presented at Table 3, patients with baseline hemoglobin level higher than 10 g/dL or baseline TSAT higher than 20% are less benefit from intravenous iron treatment. Because the baseline mean hemoglobin was  $10.7 \pm 1.5$  g/dL and the baseline mean TSAT was  $27.4 \pm 10.2\%$  in PD group, no increment of hemoglobin in this group may be explained by the high baseline hemoglobin and TSAT level. Though relatively low erythropoietin dosage ( $171 \pm 102$  IU/kg/week) was administered to PD group, the dose provided to this population was quite sufficient for patients receiving rHuEpo by the subcutaneous route because subcutaneous administration of rHuEpo is known as more effective than intravenous route.

We found that the children with both low hemoglobin and hypoferritinemia or absolute iron deficiency (low TSAT in addition to hypoferritinemia) before intravenous iron treatment showed higher increment of hemoglobin level after intravenous iron therapy than those with only hypoferritinemia. To the contrary, the children with only hypoferritinemia predicted higher increment of ferritin level after the treatment. This suggests that intravenous iron can be most effectively used in children with low baseline hemoglobin or TSAT in addition to hypoferritinemia.

Among the reported dosage of intravenous iron for iron repletion and maintaining storage [10-15], we selected 3 mg/kg/week for patients on HD. However, we were unable to find out any literature describing the dosage for pediatric PD patients confidently. Accordingly, we chose 200 mg/m<sup>2</sup> on alternate weeks considering that PD patients would be unwilling to visit hospital weekly, and to provide equivalent iron doses in both study groups. Moreover, because previous studies have revealed that a dose of 100-300 mg presents a safe dose range for adults [35-37], we limited the maximum amount of single infusion to 200 mg.

In this study, though no one revealed excessively high ferritin level, TSAT level rose over 50% in 6 patients of the PD group. Moreover, the high TSAT level persisted till week 16, 10 weeks after the last intravenous dose in one patient. Though there was no evidence that transiently high TSAT level in these patients was associated with any adverse, iron-mediated effects, we think that it may be undesirable to expose the patients to risks of iron overload. Therefore, we assume that the dosage used in PD group in this study (200 mg/m<sup>2</sup> every other week) was relatively high, and would recommend that a lower initial dosage of iron sucrose for PD patients may be preferable.

Though our study is a prospective study, this study has limitation of a single-center and non-controlled study with insufficient number of patients. Relatively low rHuEpo dosage in some patients by the regional health insurance policy was another shortcoming leading to unsatisfactory conclusion about the efficacy of the intravenous iron treatment. In addition we failed to present an ideal intravenous iron sucrose dose for children

on PD. However, this study demonstrated that intravenous iron sucrose is effective in improving iron status in children on chronic dialysis, particularly when hypoferritinemia is combined with low hemoglobin or TSAT, and that it is relatively safe. Our experience could also propose an unacceptable range of intravenous iron sucrose dosage for children on PD.

### Acknowledgement

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### 요 약

#### 한국 만성 투석 소아 환자에서 정맥용 철분 제제 투여에 관한 연구

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**목적** : 소아에서 정맥용 철분 제제 투여에 대해서는 활용할 수 있는 연구 결과가 제한되어 있다. 이번 연구에서는 만성 투석 환자에게 정맥용 철분 수크로스 제제를 투여함에 있어서 효과 및 결과 예측 인자, 안정성을 확인해 보고자 한다.

**방법** : 혈청 페리틴 농도가 100 ng/mL 이하이거나 트랜스페린 포화도가 20% 이하인 21명의 만성 투석 환자가 선정되었다. 12명의 복막 투석 환자에게 철분 수크로스를 체표면적당 200 mg의 용량으로 2주 간격으로 4회 투여하였고, 9명의 혈액 투석 환자에게 동일한 제제를 체중당 3 mg의 용량으로 일주일 간격으로 8회 투여하였다

**결과** : 치료 후 혈청 페리틴 농도는 양측 환자에서 유의한 상승을 보였고 복막 투석 환자에서는 트랜스페린 포화도가 유의한 상승을 보였다. 그러나



혈색소 수치는 양측 환자에서 모두 의미 있는 상승을 보이지는 않았다. 기저 혈색소 수치가 10 g/dL 이하이거나 기저 트랜스페린 포화도가 20% 이하인 환자는 정맥용 철분 제제 투여 후 의미있는 혈색소 상승을 보였다. 대조적으로 기저 혈색소 수치와 트랜스페린 포화도가 높았던 환자들은 치료 후 혈청 페리틴 수치의 상승을 보였다. 심각한 부작용은 없었으나 치료하는 과정에서 6명의 복막 투석 환자에서 50% 이상의 트랜스페린 포화도를 보였다.

**결론**: 본 연구에서 혈액 투석 환아에서 일주일 간격으로 체중당 3 mg의 철분제제의 정맥 투여는 안전하게 사용될 수 있음을 확인할 수 있었던 반면, 복막 투석 환자에서 격주 간격으로 체표면적당 200 mg의 철분제제의 정맥 투여는 과도한 트랜스페린 포화도를 보일 수 있다.

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