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Low-Dose Maintenance Intravenous Iron Therapy Can Prevent Anemia in Children with End-Stage Renal Disease Undergoing Chronic Hemodialysis

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- Iron Therapy
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Abstract

Background: Anemia, a common complication of end-stage renal disease, is associated with elevated morbidity, mortality, and health care costs. A primary cause of anemia in end-stage renal disease is iron deficiency, particularly among patients requiring Hemodialysis. Therefore, the purpose of this study was to determine if IV iron maintenance treatment is helpful for avoiding anaemia in children withEnd-Stage Renal Disease(ESRD). **Methods:** This study is a randomized clinical trial and was carried out at Pediatric Dialysis Unit from March 2021 till September 2022. **Results:**there was statistically significant difference between the studied groups as regard Hb , red cell indicies (MCH, MCHC), serum iron andtransferrin saturation(TSAT) at the end of the study. **Conclusion:** IV iron maintenance therapy along witherythropoiesis-stimulating agents (ESAs) in children with ESRD who were undergoing regularHemodialysis (HD) was beneficial for maintaining hemoglobin levels and reducing the risk of anemia. This therapy should therefore be considered for this patient group. However, iron supplementation for patients with hyperferritinemia is a challenging issue because the high serum ferritin level may not confirm iron marker overload. Hence, the decision to start IV iron maintenance therapy in patients with hyperferritinemia should follow a holistic approach, taking into consideration the patient's clinical condition and morbidity.

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INTRODUCTION

Anemia is a serious consequence that frequently affects people with end-stage renal disease (ESRD) who get regular hemodialysis (HD); in kids with haemoglobin levels below 110 g/L, its frequency has been estimated to be over 93% **[1]**. According to the Korean Know-Ped CKD trial, anaemia in children with chronic kidney disease (CKD) was linked to low nutritional status and iron deficiency in 72% of cases **[2]**. This is terrible since anaemia has been linked to high morbidity and death rates as well as a poor quality of life **[3]**. According to a recent research conducted at our facility, the majority of our juvenile ESRD patients had anaemia, which may have contributed to cardiac morbidity and mortality **[4]**.

Iron repletion (an episodic iron therapy given when the patient experiences iron deficiency) and maintenance therapy (regular iron supplementation at a lower dose) are two methods of iron therapy commonly used for ESRD patients undergoing HD, according to the Kidney Disease Improving Global Outcome (KDIGO) and the Renal Association **[5, 6]**. There is insufficient solid data to suggest iron maintenance therapy for this patient population, in contrast to the iron replacement strategy **[5]**. Additionally, there is little agreement between nephrologists and haematologists about the use of intravenous (IV) iron treatment, and there is no clear advice on whether erythropoiesis-stimulating agents (ESAs) should be coadministered with iron supplements in the management of anaemia **[7]**.

Therefore, the purpose of this study was to determine if IV iron maintenance treatment is helpful for avoiding anaemia in chidren with ESRD.

Patients and methods:

This study is a randomized clinical trial and was carried out at Pediatric Dialysis Unit from March 2021 till September 2022.

The following were the inclusion criteria:Patients aged <18 years with ESRD who underwent HD for at least 3 months at the Pediatric Dialysis Unit, ferritin less than 400 µg/l, transferrin saturation (TSAT) less than 30% and on ESA therapy(Maintenance dose of erythropoietin beta incase of S.C 30 IU/KG/week

In case of IV 60 IU/ KG / week).

According to KDIGO, the following criteria were used to establish normal haemoglobin levels: 110 g/L for children aged 0.5 to 5 years, 115 g/L for kids aged 5 to 12 years, 120 g/L for kids aged 12 to 15 years, 120 g/L for females over the age of 15, and 130 g/L for boys over the age of 15 years **[5]**.

For children patients with ESRD who receive HD, the KDIGO guidelines stated that the iron need be ferritin >100 /mL and transferrin saturation (TSAT) >20% **[5]**.

The following were the exclusion criteria:C-reactive protein greater than 50 mg/l, active infection, chronic liver disease and/or screening alanine aminotransferase or aspartate transaminase more than triple normal values, advanced HF (i.e. NYHA class IV), history of acquired iron overload, previous severe hypersensitivity reactions to i.v. iron sucrose, hemolytic anemia, bleeding manifestation or hemoglobinopathy, transfer to the adult HD unit, conversion to peritoneal dialysis, or incomplete medical records and the receipt of red blood cell or whole blood transfusion during the follow-up period

Complete demographic and clinical data were obtained from the medical records of the included patients

The eligible patients were retrospectively categorized into two groups: The treatment group

that included the patients who received iron maintenance therapy and a comparison group that included the remaining patients. The treatment group patients received 2 mg/kg of IV iron sucrose every 2 weeks for two doses. The iron sucrose was diluted in 0.9% saline solution at a concentration of 1 mg/mL and was administered at a rate of 100 mL/h. The comparison group patients did not receive the iron maintenance therapy. None of the patients received oral iron therapy during the study period.

The follow-up period began when the patients achieved normal hemoglobin levels and iron status and lasted for 6 weeks. During this period, patients in both groups continued to undergo HD according to a constant regimen, in which the duration, blood flow, dialysate flow, ultrafiltration, and heparin dose had remained constant within the previous 1 month. ESAs were administered to all the patients at stable doses beginning at least 1 month prior to the study and continuing until at least the end of the follow-up period.

The primary outcome was the proportion of patients in each group who experienced anemia during the 6-week follow-up period. The secondary outcomes were changes in hemoglobin and TSAT levels. Specifically for the purposes of this study, patients were considered to have iron depletion when their hemoglobin levels were normal for their age, but their TSAT levels were <20%. Iron overload was defined as TSAT levels >50% **[8]**.

Statistical Analysis: Analysis of data was done using Statistical Program for the Social Sciences version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described in the form of mean and SD. Qualitative variables were described as number and percentage. To compare parametric quantitative variables between two groups, Student's *t*-test was performed. Qualitative variables were compared using χ^2-test or Fisher's exact test when frequencies were below five. Pearson's correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a *P* value less than 0.05 is considered significant

Results

Table (1): Comparison between studied cases according to baseline and clinical data

Age (years)	**Group A (n = 30)**		**Group B (n = 30)**		**p**
Range.	10 – 17		10 – 17		0.339
Mean ± SD.	13.5 ± 2.36		14.13 ± 2.71		
Sex	No.	%	No.	%	
Female	9	30.0	7	23.3	0.559
Male	21	70.0	23	76.7	
Comorbidities					
Glomerulopathy	12	40.0	9	30.0	0.683
Kidney hypoplasia and dysplasia	12	40.0	15	50.0	
Urological abnormalities	6	20.0	6	20.0	
Nutritional status					
Malnourished	12	40.0	19	63.3	0.071
Well-nourished	18	60.0	11	36.7	
Hemodialysis access					
Arteriovenous fistula	2	6.7	3	10.0	0.640
Tunneled catheter	28	93.3	27	90.0	

SD: **Standard deviation**
χ^2: **Chi square test** t**: Student t-test**
p: p value for comparing between studied groups
*: Statistically significant at $p \leq 0.05$
Group A: The treatment group that included the patients who received iron maintenance therapy
Group B: The comparison group patients did not receive the iron maintenance therapy.
This table shows that there was no statistically significant difference between the studied groups as regard baseline and clinical data.

Table (2): Comparison between studied cases according to baseline lab

	Group A (n = 30)	**Group B (n = 30)**	**p**
Hb (g/L)			
Range.	112 – 140	110 – 140	0.832
Mean ± SD.	126.43 ± 7.74	125.97 ± 9.16	
MCV (fL)			
Range.	82.5 – 90.1	82.4 – 89.9	0.313
Mean ± SD.	86.86 ± 2.25	86.3 ± 2.01	
MCH (pg/cell)			
Range.	27.2 – 29.8	27.3 – 29.9	0.424
Mean ± SD.	28.72 ± 0.67	28.87 ± 0.77	
MCHC (g/L)			
Range.	323 – 338	323 – 338	0.249
Mean ± SD.	329.8 ± 4.17	331.1 ± 4.47	
Relative reticulocyte count			
Range.	0.02 – 0.02	0.02 – 0.02	0.524
Mean ± SD.	0.02 ± 0	0.02 ± 0	
serum iron (µmol/L)			
Range.	9.9 – 16.5	9.8 – 16.7	0.665
Mean ± SD.	13.47 ± 2.02	13.71 ± 2.25	
TIBC (µmol/L)			
Range.	32.4 – 41.8	32.7 – 41.3	0.575
Mean ± SD.	37.32 ± 3.04	36.91 ± 2.57	
TSAT (%)			
Range.	28.4 – 51.8	28.2 – 51.4	0.653
Mean ± SD.	39.28 ± 7.15	40.1 ± 6.97	
Ferritin (µg/L)			
Range.	728 – 1512	776 – 1495	0.942
Mean ± SD.	1127.3 ± 219.1	1123.3 ± 206.43	

SD: **Standard deviation**
F: Oneway ANOVA test **H: Kruskal-Wallis test**
t: Paired t-test **Z: Wilcoxon test**
p: p value for comparing between studied groups
p: p value for comparing between day 1 and day 7
*: Statistically significant at $p \leq 0.05$
Group A: The treatment group that included the patients who received iron maintenance therapy
Group B: The comparison group patients did not receive the iron maintenance therapy.

This table shows that there was no statistically significant difference between the studied groups as regard baseline lab.

Table (3): Comparison between studied cases according to lab at the end of study

	Group A (n = 30)	Group B (n = 30)	p
Hb (g/L)			
Range.	110 – 137	101 – 132	<0.001*
Mean ± SD.	125 ± 7.17	114.4 ± 8.98	
MCV (fL)			
Range.	81.4 – 91.6	82.7 – 90.2	0.661
Mean ± SD.	86.76 ± 2.62	86.49 ± 2.16	
MCH (pg/cell)			
Range.	26.9 – 33	25.6 – 31.3	0.014*
Mean ± SD.	29.71 ± 1.87	28.68 ± 1.24	
MCHC (g/L)			
Range.	321 – 343	318 – 333	<0.001*
Mean ± SD.	331.6 ± 5.22	325.47 ± 4.28	
Relative reticulocyte count			
Range.	0.02 – 0.03	0.01 – 0.03	0.864
Mean ± SD.	0.02 ± 0	0.02 ± 0	
serum iron (µmol/L)			
Range.	10.4 – 17.4	6.9 – 16.5	<0.001*
Mean ± SD.	14.41 ± 2.13	11.96 ± 2.45	
TIBC (µmol/L)			
Range.	31 – 41.2	31 – 40.9	0.445
Mean ± SD.	36.36 ± 3.26	35.79 ± 2.49	
TSAT (%)			
Range.	31.2 – 52.4	23.4 – 48.1	0.022*
Mean ± SD.	41.09 ± 7.2	36.66 ± 7.32	
Ferritin (µg/L)			
Range.	863 – 1624	903 – 1680	0.914
Mean ± SD.	1262.13 ± 215.58	1255.9 ± 229.68	

SD: **Standard deviation**

F: Oneway ANOVA test **H: Kruskal-Wallis test**

t: Paired t-test **Z: Wilcoxon test**

p: p value for comparing between studied groups

p: p value for comparing between day 1 and day 7

*: Statistically significant at $p \leq 0.05$

Group A: The treatment group that included the patients who received iron maintenance therapy

Group B: The comparison group patients did not receive the iron maintenance therapy.

This table shows that there was statistically significant difference between the studied groups as regard Hb, MCH, MCHC, serum iron and TSAT at the end of the study.

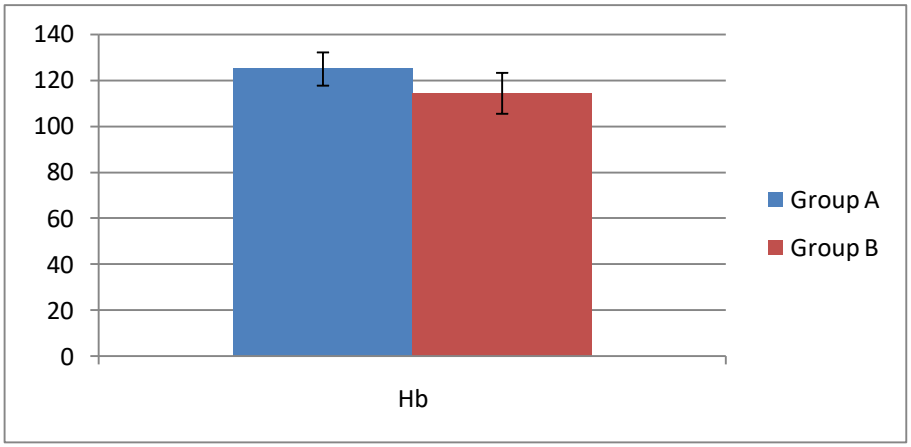

Fig (1): Comparison between studied cases according to Hb at the end of study

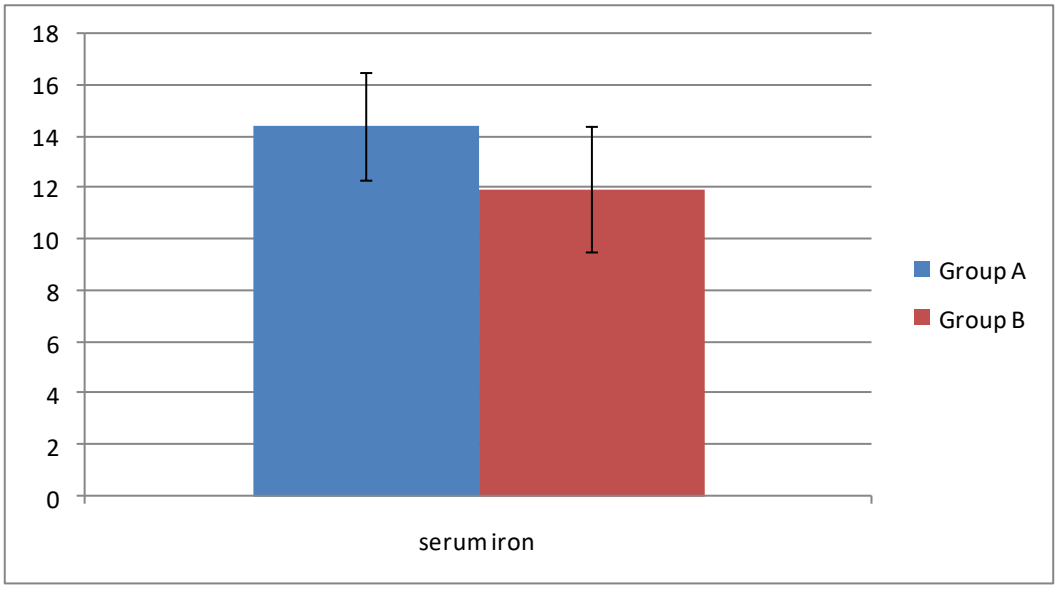

Fig (2): Comparison between studied cases according to serum iron at the end of study

Discussion

Anemia, a common complication of end-stage renal disease, is associated with elevated morbidity, mortality, and health care costs. A primary cause of anemia in end-stage renal disease is iron deficiency, particularly among patients requiring HD **[9].**

It was reported that anemia in pediatric chronic kidney disease (CKD) was associated with poor nutritional status and 72% had iron deficiency **[10].** This is devastating because anemia is known to be associated with low quality of life, in addition to high morbidity and mortality. A recent study from our center revealed that most of our pediatric ESRD patients had anemia, leading to cardiac morbidity, and may have contributed to death **[11].**

IV iron is an effective way to supplement iron and optimize erythropoiesis. Existing randomized controlled trials showed that supplementing ESA therapy with i.v. iron increases hemoglobin production and lowers ESA requirement. Consequently, co-administration of ESAs and i.v. iron has become the primary management strategy for anemia in HD patients **[12].**

Bailie and colleagues reported that the percentage of i.v. iron use rose from 1999 to 2011 in most countries and varied widely by country; in Japan, it was 36%, but among the other countries, the use ranged from 70% in Australia–New Zealand to 90% in Belgium **[13].**

Reduced ESA use afforded by higher doses of iron may reduce the risk of cardiovascular events observed in the aforementioned trials **[14].** Independent of ESA use, dialysis patients are at high risk for cardiovascular events, and there is also strong evidence in patients with HF, documenting improvements in symptoms and in left ventricular systolic function with i.v. iron repletion **[15].**

The aim of this study, therefore, was to identify whether IV iron maintenance therapy with ESAs is beneficial for preventing anemia in children with ESRD.

In this study we demonstrated that there was no statistically significant difference between the

studied groups as regard baseline and clinical data.

This was concordant with **Szczech et al. [16]** who reported that there was no statistically significant difference between the studied groups regarding age and sex distribution.

Ibrahim et al. [17] found that there was no statistically significant difference between the studied groups regarding age and sex distribution.

Also, **Ambarsari et al. [18]** found that among 41 pediatric patients, of which 21 received IV iron maintenance therapy (the treatment group), whereas the other 20 patients did not (the comparison group), there were no significant differences in the baseline characteristics between the groups.

In this study we illustrated that there was statistically significant difference between the studied groups as regard Hb, MCH, MCHC, serum iron and TSAT at the end of the study.

Ambarsari et al. [18] found that in the treatment group, hemoglobin levels were maintained within the normal range, with a mean difference between baseline and final hemoglobin levels of 0.7 g/L (95% CI, −6.6 to +8.0 g/L; p=0.83). Conversely, the comparison group experienced a significant reduction in hemoglobin levels by 21 g/L (95% CI, 9.3–33 g/L; p=0.001).

In a randomized clinical trial, **Ruiz-Jaramillo et al. [19]** compared two groups of children with ESRD who were undergoing HD and had either absolute or functional iron deficiency. The first group received iron therapy consistent with their ferritin level, starting with a loading dose, followed by weekly maintenance doses until achieving TSAT >50% and ferritin >800 μg/L. The second group received an intermittent dose for 10 weeks. The study revealed that iron maintenance therapy based on serum ferritin levels was better than administering intermittent doses for achieving the desired hemoglobin and ferritin levels, with a smaller risk of iron overload.

In a study by **Rottembourg et al. [20],** two groups of adult patients with renal failure received either IV iron therapy prior to the initiation of HD or no IV iron therapy. Both groups received 50 mg/week of IV iron therapy during their HD treatment, in addition to ESAs. The hemoglobin and TSAT levels were compared between the initiation of HD and 12 months later. The study results showed that, for ESRD patients undergoing regular HD, IV iron therapy with maintenance dosing administered concomitantly with ESAs improved hemoglobin and TSAT levels, in both the patients who initially had low levels of hemoglobin and/or TSAT and the patients who initially had normal levels of hemoglobin and/or TSAT.

A study in an adult population by **Peters et al.[21]** showed that IV iron maintenance therapy with a very low dose (15.56 ± 42.4 mg/week) resulted in a significant reduction in TSAT only after a 3-month observation. Another possible reason for the low TSAT levels despite the elevated ferritin levels may have been the hepcidin-mediated blockade of iron mobilization from the reticuloendothelial system

In a randomized clinical trial that included subjects with similar age characteristics to those in the present study, **Goldstein et al. [22]** administered one of three doses of IV iron sucrose (0.5, 1.0, or 2.0 mg/kg) to patients aged 2–20 years once every other week for six doses. The maintenance dose of 2 mg/kg/2 weeks achieved a success rate of 43% for maintaining hemoglobin levels of ≥10.5 g/dL and TSAT ≥20%.

The present study provides valuable new data on the role of IV iron maintenance therapy on anemia in pediatric patients with ESRD who undergo regular HD. Until now, there has been a lack of evidence for this approach. The study demonstrated the effects of IV iron maintenance therapy in maintaining hemoglobin levels and preventing anemia. It also showed that there is the possibility that pediatric patients may develop iron overload, despite the low doses of IV iron, and that administering IV iron maintenance therapy to pediatric patients undergoing chronic HD who had high ferritin levels did not necessarily result in clinically relevant iron toxicity, so providing iron therapy to this patient group with high ferritin levels could be beneficial for preventing anemia without side effects.

However, the study had some limitations. The small number of subjects and short follow-up period in this study limited the ability to adjust for other risk factors or for confounding factors on anemia. In addition, we were unable to evaluate the effect of long-term IV iron maintenance therapy on the morbidity and mortality of the patients.

Conclusions

IV iron maintenance therapy along with ESAs in children with ESRD who were undergoing regular HD was beneficial for maintaining hemoglobin levels and reducing the risk of anemia. This therapy should therefore be considered for this patient group. However, iron supplementation for patients with hyperferritinemia is a challenging issue because the high serum ferritin level may not confirm iron marker overload. Hence, the decision to start IV iron maintenance therapy in patients with hyperferritinemia should follow a holistic approach, taking into consideration the patient's clinical condition and morbidity.

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