ORIGINAL ARTICLE

PARENTERAL IRON SUCROSE IN IRON DEFICIENCY ANAEMIA OF PAEDIATRIC CHRONIC KIDNEY DISEASE

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Background: Erythropoietin (Epo) and iron therapy plays a major role in the management of renal anaemia. Iron sucrose (IS) has been used to treat iron deficiency anaemia (IDA) and to maintain adequate iron store in chronic kidney disease (CKD). The objective of the study was to determine the response and safety of IS in the treatment of IDA. **Methods:** This retrospective study was carried out in the Department of Nephrology, National Institute of Child Health, Karachi from Dec 2008 to Dec 2010. Children aged 6 months to 14 years, CKD-stage 2–5, and IDA were included. Pertinent data including age, gender, serum creatinine (SCr), CKD-stage, aetiology, treatment mode, IS dose, pre- and post-treatment parameters and side effects were collected and analysed. **Results:** Among 35, majority (66%) were boys. Mean age was 6.97±4.13 years and mean SCr was 3.78±3.1 mg/dl. Majority were in CKD-stage 4–5 and treated conservatively. Major aetiologies were hypoplasia-dysplasia (40%), juvenile nephronophthiasis (17.14%), posterior urethral valves, and stones. Baseline mean Hb and Transferrin Saturation (TS) was 7.38±1.38 g/dl and 11.19±5.28% respectively. Mean Hb increased to 9.22±16.32 g/dl with correction of iron deficit (p<0.001) and a sustained rise in Hb was observed after Epo and maintenance iron sucrose. Mean TS% increased to 49.13±18% (p<0.001). No major side effects were observed except iron overload. **Conclusion**: Iron sucrose was effective in improving IDA in CKD without significant side effects. Iron sucrose may be used to treat IDA with monitoring for iron overload.

Keywords: Iron deficiency, anaemia, iron sucrose, chronic kidney disease

INTRODUCTION

Paediatric chronic kidney disease (CKD) is an irreversible progressive inflammatory disease associated with high morbidity and mortality. It accounts for 12–14% of renal diseases in tertiary care centres in Pakistan.[1,2] Anaemia has been associated with increased mortality and increased risk of hospitalisation.[3,4]

Renal anaemia appears early and its severity increases progressively with decline in estimated glomerular filtration rate (eGFR) to <60 ml/min/1.73 m^2. Prevalence of anaemia is 36.6% and it increases from 31% in early stages to 93.3% in advanced CKD.[5] National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines recommend initiation of workup for anaemia when Hb falls <5th percentile for age and sex. NKF-KDOQI guidelines also recommend use of erythropoietin stimulating agents (ESAs) like recombinant human Epo for treatment of renal anaemia when Hb falls to <11g/dl and maintaining a target Hb at 11–12 g/dl.[3,4]

Studies have shown that maintaining Hb at ≥11 g/dl results in not only improved quality of life but decreases hospitalisation rates, transfusion need and mortality.[6–9] Though use of ESAs and parenteral iron therapy have changed the outcome of renal anaemia but its management still remains a challenge.[4,7–10] Studies have also shown that iron supplementation during ESAs treatment may decrease the requirement of Epo in both adults and children.[5,11]

Erythropoietin and iron deficiencies are the two major causes of anaemia.[7,10,11] Other contributing factors include vitamin B_{12} and folate deficiency, hyperparathyroidism and inflammatory mediators (IL-6, IL-1, TNFα) which inhibit erythropoiesis.[5,7,11,13]

Iron deficiency (ID) is an important contributor to renal anemia.[7] It may be absolute or functional ID and needs iron replacement for adequate Epo response.[7,11,13] ID may also develop during ESAs therapy due to increased iron demand for active erythropoiesis. This functional ID may also result in poor response to ESAs and need parenteral iron therapy.[11,13–15] Iron regulatory hormone, hepcidin plays a critical role in the pathogenesis of renal anaemia.[18,19] Hepcidin level is increased in response to iron overload to decrease intestinal iron absorption and iron release from stores whereas its low level in ID leads to enhanced iron absorption and iron release from stores.[13,18–21] Chronic inflammatory states trigger IL-6 production which increases hepcidin level leading to iron sequestration within macrophages and restricted iron release.[4,18–21] High hepcidin levels may contribute to higher incidence, more severe anaemia, and even resistance to ESAs.[13,18–22] Furthermore, macronutrient and micronutrient deficiencies including iron are prevalent (65%) in developing countries.[17] Though, oral iron is commonly used to treat IDA since it is cheap, convenient and safe but insufficient to maintain iron stores.[4,11,22]

Parenteral iron has been used to treat IDA in patients on haemodialysis (HD) and peritoneal dialysis (PD) with improved iron status, Hb level and less Epo dosage.[4,11,14,22] However, anaemia still remains partially corrected due to both absolute and functional ID and

inflammatory blockage (effects of hepcidin). This functional and inflammatory block require higher doses of Epo than its physiological dose.[13,14,20]

Though NKF-DOQI guidelines recommend serum ferritin level <100 ηg/ml and TS% <20 for defining IDA in CKD, we in this study used TS% ≤20 as iron deficiency since serum ferritin is highly unreliable.[3,4,11,13,18–22] Parenteral IS has been used safely to treat ID in pediatric CKD in developed countries but experience of such therapy has not been reported in Pakistan. Thus objective of this study was to determine the response and safety of parenteral iron sucrose (PIS) in treatment of IDA in paediatric CKD.

MATERIAL AND METHODS

This retrospective study was carried out in the Department of Paediatric Nephrology, NICH, Karachi from Dec 2008 to Dec 2010. Children aged 6 months to 14 years with CKD stage 2–5 (eGFR<90 ml/min/1.73 m^2) and IDA defined as Hb<11g/dl and TS≤20% were included. Iron overload was defined as TS>50%. Patients with CKD-stage 1, Hb>11 g/dl and TS>20% were excluded. Informed parental consent was taken before enrolment.

Based on eGFR the disease severity was classified into 5 stages: 1= >90 ml/min/1.73 m^2, 2=60–89, 3=30–59, 4=15–29 5=<15 ml/min/1.73m^2.[3] Indications for IS were inadequate or no response to oral iron sulphate (4–5 mg/Kg/day) for 3 months, poor response to Epo while on oral iron, those who developed ID after Epo therapy, and with poor compliance.

Iron sucrose was given intravenously after test dose over 2–3 hours (2.5–7 mg/Kg/dose) dissolved in normal saline (1 mg/ml) on alternate days with strict monitoring till deficit was corrected and then continued as weekly maintenance dose. Erythropoietin was given subcutaneously (100–200 U/Kg/dose) 1–2/week once iron deficit was corrected. Response to IS was assessed by Hb at monthly intervals for 3 months and by TS% after 3 months.

Data including age, gender, SCr, eGFR and CKD-stage, aetiology, treatment mode (dialysis or conservative), oral iron use, indications for PIS, pre- and post-IS treatment Hb levels, TS% and side effects if any were recorded on special performa. Data was analysed using SPSS-16. Qualitative variables like sex, aetiology and CKD-stage were represented by frequencies and percentages. Mean±SD was calculated for quantitative variables like age, Hb and TS%. Shapiro-Wilk test was applied to determine normality of the data. Independent sample *t*-test was used to determine significant differences between both the gender's pre and post parameters. Paired *t*-test was applied to determine significant differences between baseline and post treatment parameters for both male and female; $p<0.05$ was taken as significant. ANOVA was used to find significant differences in Hb levels at three months.

RESULTS

Among 35 children with IDA, 23 (66%) were boys and 12 (34%) were girls. Baseline clinical and laboratory characteristics are shown in Table-1. Mean Hb and TS% was 7.38±1.38 g/dl and 11.19±5.28% respectively. Most common (34.3%) age group was 1–5 years.

Table-2 shows stages of severity of CKD and almost 80% had advanced disease (Stage 4–5). Majority (71.4%) were on conservative treatment whereas 10 (28.6%) were on HD (Table-1). Majority (32) of children received oral iron whereas only 3 were put on PIS directly.

The underlying aetiologies for CKD (Table–3) were hypoplasia-dysplasia (14, 40%), juvenile nephronophthiasis (6, 7.14%), posterior urethral valves, and stone disease (each 11.42%).

Indications for PIS were no response to oral iron after 3 months (15, 42.9% and poor response to Epo while on oral iron (7, 20%) whereas 6 (17.1%) developed functional ID after Epo therapy. Poor compliance to oral iron (4, 11.4%) and 3 received PIS without oral iron trial due to poor compliance.

Table-4 shows that mean iron deficit was 466.5±28 mg/dl, mean IS-dose/patient/day was 67.71±30.34 mg and mean duration of treatment was 2.86±2.36 weeks.

Table–5 shows response to iron sucrose with respect to pre and post-treatment parameters. Use of iron sucrose improved Hb significantly from baseline 7.38±1.38 to 9.22±1.32 g/dl with correction of iron deficit and sustained rise in Hb was continued with introduction of Epo and on maintenance IS dose as shown by serial Hb levels at 1, 2 and 3 months as 9.02±1.42 g/dl, 9.56±1.33 and 10.43±1.42 g/dl respectively ($p<0.001$). Mean TS% increased from baseline of 11.19±5.28% to 49.13±18 significantly after IS use ($p<0.001$).

Table-6 shows the comparative response to iron sucrose according to gender. There was no significant difference between two groups ($p>0.05$). No significant side effects were noted except vomiting (4), headache, tachycardia (2) and fever in one. Iron overload was observed in 22.87% of cases.

Table-1: Baseline characteristics (n=35)

Characteristics	Mean±SD	Range
Age (Years)	6.97±4.13	0.5–14
Weight (Kg)	16.50±9.44	5–38
Serum Creatinine (mg/dl)	3.78±3.106	0.5–12
eGFR (ml/min/1.73m^2)	24.31±16.8	4.4–72
Baseline Haemoglobin (g/dl)	7.38±1.38	5–10
Baseline TS%	11.19±5.28	1.36–20.7
Treatment Mode		
Haemodialysis	10	28.6%
Conservative	25	71.4%

Table-2: Stages of chronic kidney disease (n=35)

Stages of Severity	Number	Percentage
Stage-1	–	-
Stage-2	2	5.71
Stage-3	5	14.29
Stage-4	14	40.0
Stage-5	14	40.0
Mean S Cr 3.78±3.1 mg/dl & eGFR 24.31±16.8 l/min/1.73 m^2		

Table-3: Aetiology of chronic kidney disease (n=35)

Cause	Number	Percentage
Hypoplasia -dysplasia	14	40.0
Juvenile Nephronophthiasis	6	17.4
Posterior Urethral Valves	4	11.43
Stone Disease	4	11.43
Neurogenic bladder	3	8.57
Other	4	11.43

Table-4: Iron deficit, dosage and duration of Iron Sucrose treatment (n=35)

Iron Parameters	Mean±SD	Range
Total iron deficit (mg)	466.5±280.6	67.50–1400.0
Iron sucrose dose (mg/Kg/dose)	4.11±1.31	2.63–7.14
Iron sucrose dose (mg/day/)	67.71±30.34	15.00–100.0
Total number of doses	6.97±2.25	3.00–14.0
Duration (weeks)	2.86±2.366	1.00–12.0

Table–5: Response to iron sucrose treatment (n=35)

Variables	Mean±SD	*p*-value
Baseline Hb (g/dl)	7.38±1.39	
Post-treatment Hb (g/dl)*	9.22±1.34	$p<0.001$
Hb (g/dl)at 1st month	9.02±1.42[a]	
Hb (g/dl) at 2nd month	9.56±1.33[b]	
Hb (g/dl) at 3rd month	10.43±1.42[a,b]	$p<0.001$
Baseline TS%	11.19±5.28	
Post-treatment TS%	49.14±18.09	$p<0.001$

*Hb after correction of iron deficit. Variables containing same letters in superscript are significantly different from each other.

Table-6: Response to iron sucrose treatment according to gender (n=35)

Gender	Parameters	Pre-treatment	Post-treatment
Male	Hb (g/dl)*	7.43±1.34	9.45±1.40
	TS (%)*	10.18±0.75	47.73±16.05
Female	Hb (g/dl)*	7.28±1.52	8.77±1.14
	TS (%)*	13.14±0.90	51.84±22.01

*Significant difference exist between pre- and post-treatment parameters for both male and female ($p<0.05$).

DISCUSSION

Anaemia is one of common treatable complications of CKD with erythropoietin and iron deficiencies being the major causes.[5–7] With the use of recombinant human Epo, blood transfusion needs and hospitalisation have dramatically reduced.[3–5] However, to achieve optimal effects of Epo treatment in renal anaemia, it requires detection and treatment of ID prior to starting the Epo. Supplementation of iron and monitoring iron status to detect ID during Epo therapy in pre-dialysis and on dialysis has been recommended by NKF-KDOQI guidelines and by many other studies as a standard practice.[5,7,11–13]

Despite the widespread Epo usage, >50% patients do not achieve the target Hb levels (11–12 g/dl).[12,21,22] The most common reason for failure to achieve the target Hb with Epo therapy is IDA.[7,10,11] High cytokines and hepcidin levels are among the other important causes of severe anaemia and failure to achieve the optimal response.[4,13,18–20]

PIS is frequently used to treat renal anaemia and is effective in raising Hb, and maintaining iron status while on ESAs therapy.[7,14,15,22]

This study on the use of iron sucrose in the correction of IDA in CKD patients is of unique importance since intravenous iron is not practiced in IDA in our country. This could be due to effective oral iron absorption and associated potential adverse reactions with parenteral use.[7,17]

This study highlights the prevalence of severe renal anaemia (7.38 g/dl) which is comparable to 8.2 g/dl in a recent local study.[23] The mean age of 6.97 years in this study is comparable to 7.68 and 6.9 years reported by ItalKid project and Akhtar N *et al*.[16,23] Our study highlights the delayed diagnosis of CKD as evident by the fact that majority (80%) had advanced CKD indicating the late referral to Paediatric Nephrology Services. This is also comparable with Akhtar N *et al*.[23] In our study, there were 10 (28%) patients on HD indicating more advanced CKD and associated severe anaemia.[7,5,10,11] The significant contribution of congenital causes like renal hypoplasia-dysplasia (40%) may be reasons for delayed diagnosis since both of these disorders, may have nonspecific symptoms.

This study also reflects that oral iron therapy is ineffective in majority (62.9%) of patients whereas 17% developed functional ID during Epo therapy. Failure of oral iron could be due to hepcidin induced poor absorption or cytokine induced blockage of stored iron release as well as poor compliance which was documented in 20% in our study. The inadequate response to oral iron has been documented by many studies with similar reasons.[7,13–15]

Parenteral iron has emerged as an important tool in renal anaemia management either alone or in combination with Epo.[7,13] In our study, iron sucrose was effective in increasing Hb from 7.38 to 9.22 g/dl with deficit correction ($p<0.001$). Sustained level (9.22–10.6 g/) was maintained with Epo and IS.[11] Iron sucrose has increased the mean TS% from 11.19 to 49.13% in this study ($p<0.05$). This significant rise in TS% indicates that IS is effective in correcting iron deficiency. These effects on Hb and TS were equally observed in boys and girls. Thus, iron sucrose can maintain iron status during Epo therapy and may also decrease the need of Epo-dosage as reported by Gotloib L *et al*, and others.[7,11,14,22]

We did not consider the serum ferritin as reliable biomarker of iron status since many of our patients had very high ferritin but TS% was <20. So, we took TS% as the reliable indicator of IDA in this study.[7,11–14] This concern has been raised in many

studies and suggested that hepcidin could be best indicator and novel tool for assessing and monitoring iron status in near future.[13,18–22]

IDA is rampant in paediatric population of developing countries like India and Pakistan. Reported prevalence of IDA varies from 33 to 98% and figures of iron deficiency are almost similar for Pakistan (64%) and India (62%).[17,21] Recently, iron sucrose and sorbitol have been used safely and effectively in IDA without significant side effects.[24,25] However, a significant iron overload was noted after IS use which could be attributed to intercurrent infections, transfusions, hyperparathyroidism, inadequate or no dialysis and inflammatory cytokines. These factors significantly contribute to anaemia and iron overload in CKD.

CONCLUSION

Parenteral iron sucrose is effective in improving and maintaining haemoglobin and iron status in IDA of CKD. We recommend parenteral iron sucrose to treat IDA rather than oral iron in CKD. However, regular monitoring for iron overload is needed in such cases.

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