Prevalence and severity of anemia in pediatric hemodialysis patients

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ABSTRACT

Objective: To determine the prevalence and severity of anemia, and to identify independent predictors for anemia in children on hemodialysis.

Method: We conducted this cross sectional study on 25 children aged 7–20 years receiving hemodialysis from September 2005 to January 2006 in Isfahan University of Medical Sciences, Isfahan, Iran.

Results: A total of 22 (82%) patients had hemoglobin (Hb) level of <11 g/dL (anemia) and 12 (48%) patients had Hb values <8 g/dL (severe anemia). The mean age was 15.5 ± 3.7 years. Mean time on hemodialysis was 20.44 ± 15.25 months. Anemia was more common and severe among children who were on dialysis <6 months. There was an inverse relation between severity of anemia and duration of hemodialysis (r=-0.465, *p*=0.019). Nearly all patients were treated with recombinant human erythropoietin (rHuEPO). Children with severe anemia received a slightly higher dose of erythropoietin (r=0.202 *p*=0.09). There was a correlation between serum albumin and Hb level (r=0.511, *p*=0.01). Intact parathyroid hormone (iPTH) levels were >200 pg/mL in 16 patients (66%) and >400 pg/mL in 9 patients (37.5%). There was a reverse correlation between iPTH level >200 pg/mL and Hb level (r=-0.505, *p*=0.046).

Conclusion: The prevalence of anemia in our study appears to be higher than that reported in the other studies in spite of extensive use of rHuEPO and iron supplementation. We found this to be especially true for patients who were on dialysis <6 months and with low albumin and severe hyperparathyroidism.

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Anemia is a major complication of end-stage renal disease (ESRD) in children.[1] Severe anemia is associated with cardiovascular dysfunction, cardiomyopathy, and death.[2] Correction of anemia in children with ESRD improves cardiac dysfunction and exercise tolerance and reduces left ventricular hypertrophy.[2] Approximately 25% of adult patients maintained on chronic hemodialysis have anemia defined by the National Kidney Foundation Dialysis Outcome Quality Initiative (K/DOQI) as a hemoglobin (Hb) value less than 11 g/dL.[3] Upwards of 75% of children with anemia maintained on chronic hemodialysis exhibit signs of left ventricular hypertrophy, a harbinger of cardiovascular morbidity in adulthood.[4]

The major cause of anemia in patients with chronic kidney disease and ESRD is erythropoietin (EPO) deficiency resulting from decreased production by the kidneys.[2] The remarkable development and subsequent introduction of recombinant human erythropoietin (rHuEPO) in 1989 made it possible to safely and effectively treat the anemia of renal insufficiency and practically eliminate the need for repeated transfusions.[5] Despite the advances in dialysis care and the use of erythropoietin, anemia continues to be a clinical problem seen in patients with ESRD.[3] It was believed that iron deficiency was the major predictor of EPO hyporesponsiveness.[6] Frankenfield et al[3] reported that in spite of extensive use of EPO and prescribed iron supplements, over one third of children maintained on chronic hemodialysis have a mean Hb of less than 11 g/dL. Other factors that have been shown to influence the response to rHuEPO in adult and pediatric dialysis patients include dosage, route of administration, acute or chronic infection and aluminum intoxication.[1] Secondary hyperparathyroidism contributes to resistance to rHuEPO in adults.[1] Belsha and Berry[1] revealed that when serum parathyroid hormone (PTH) levels were markedly elevated in pediatric patients on dialysis, response to rHuEPO might be poor.[1]

The objectives of this study were 1. to determine the prevalence and severity of anemia in children and adolescents on chronic hemodialysis 2. to identify independent predictors for anemia in children on hemodialysis.

Methods. This cross-sectional study was conducted at the Department of Pediatrics, Isfahan University of Medical

Sciences, Isfahan, Iran between September 2005 and January 2006. Local institutional committee approved the study protocol.

Twenty-five children with ESRD receiving hemodialysis were enrolled in this study. All the patient-specific parameters were recorded, including age, gender, pre and post dialysis body weight, height, body mass index (BMI), etiology of ESRD, duration of dialysis (6 months versus 6 months or longer) and access type. Blood studies were performed immediately on pre dialysis. The laboratory tests included: Hb, hematocrit, reticulocyte count, serum unconjugated bilirubin, lactic dehydrogenase, direct Coomb's test, blood urea nitrogen (BUN), serum iron, ferritin, total iron binding capacity (TIBC), calcium, phosphate, intact parathyroid hormone (iPTH), albumin, alkaline phosphatase and C reactive protein (CRP). Another blood sample for BUN was taken 30 minutes after dialysis session. Data on patient rHuEPO dose and oral or intravenous iron dose were obtained from dialysis charts. Serum iPTH and ferritin (ng/mL) were measured by a chemiluminescence immunoassay.

Anemia was defined as follows: Hb <11 g/dL and severe anemia as Hb <8 g/dL. Iron deficiency was defined as follows: ferritin ≤100 ng/dL or transferrin saturation <20% and mean corpuscular volume (MCV) <75 fL.

Serum iPTH >200 pg/mL was considered as high turn over bone disease. Urea reduction rate (URR) and Kt/V values were calculated using Lowrie and Lew formula and Daugirdas 2 formula respectively. Adequate dialysis clearance was defined as Kt/V ≥1.2 and URR ≥65%. Estimated normalized protein catabolic rate (EstNPCR) was calculated by Borch equation to estimate the daily protein intake. An EstNPCR <0.8 g/kg/day was considered as malnutrition.

The results were analyzed using the Statistical Package for Social Sciences (version 11.5) program and expressed as mean and standard deviation. Statistical analysis of data was performed by Spearman and Pearson tests to show correlation between anemia and other variables. Differences at the level of $p<0.05$ were considered to be statistically significant.

Results. The study group was composed of patients aged 7–20 years (3 patients were less than 12 years old). The mean age of hemodialysis patients was 15.5 ± 3.7 years. There were 13 female (52%) and 12 male (48%). Mean duration of hemodialysis was 20.4 ± 15.2 months (1-48 months). Hemodialysis access was by arteriovenous graft (1 patient), Arteriovenous (AV) fistula (15 patients), permanent right arterial catheter (8 patients) or temporary right arterial catheter (1 patient). The AV fistula was more commonly used as access in anemic children. Five patients (20%) had a previous history of transplantation. The etiologies of graft loss were infection, noncompliance and chronic allograft nephropathy.

The baseline renal diagnosis included chronic glomerulonephritis (4 patients) nephronophthisis (2 patients) obstructive uropathy (2 patients), reflux nephropathy (2 patients) focal segmental glomerulosclerosis (2 patients) Alport syndrome (1 patient) systemic lupus erythematosus (1 patient), Henoch-Schonlein purpura (1 patient), renal dysplasia (1 patient) polycystic kidney disease (1 patient) single kidney and posttraumatic nephrectomy (1 patient) neurogenic bladder with secondary reflux nephropathy due to spinal injury (1 patient) and unknown etiology (6 patients).

Table 1 summarizes major characteristics and selected laboratory findings. Twenty-two patients (88%) had Hb values <11 g/dL and 48% (12 patients) had Hb values <8 g/dL. There was evidence of hemolytic anemia in 2 patients. The platelet count was normal in these 2 cases. Four patients (16%) had megaloblastic anemia and all of them were hypoalbuminemic (albumin <3.5 g/dL). No statistically significant relation was found between age, gender and Hb level (r=0.216, p=0.30; r=-0.236, p=0.290 respectively).

Anemia was more common among children who were maintained on dialysis <6 months (6 of 6 patients) (100%) compared to children dialyzing 6 months or longer (16 of 19 patients) (83%). Anemia was more severe in patients who were on dialysis <6 months (5 of 6 patients) (83%) compared to children dialyzing 6 months or longer (7 of 16 patients) (43%). There was an inverse relation between severity of anemia and duration of hemodialysis (r=-0.465, p=0.019) (**Figure 1**). Nearly all children (92%) were treated with EPO with no differences between the routes of administration. Children with more severe anemia received a slightly higher dose of EPO (r=0.202, p=0.09). There was no correlation between EPO dose and Hb level (r=-0.180, p=0.410). Children with anemia received higher weekly EPO doses (167.19 ± 86.61 units/kg/week) versus children with Hb level >11 g/dL (101.03 ± 19.36 units/kg/week), (p=0.21); and children with severe anemia received higher weekly EPO (161.85 ± 73.36 units/kg/week) versus children with mild to moderate anemia (173.71 ± 104.88 units/kg/week) (p=0.44).

A total of 31% of anemic children had a transferrin saturation (TSAT) <20%. Absolute iron deficiency was only seen in one patient. Five patients (20%) were not treated with iron preparations. Six patients were treated with intravenous iron and their mean iron dose was 4.05 ± 2.29 mg/kg/wk and 14 patients were treated with oral preparations and their mean iron dose was 2.09 ±

1.28 mg/kg/wk. However, no statistically significant relation was found between intravenous iron dose, oral iron dose and Hb level (r=-0.657, p=0.156; r=-0.357, p=0.210 respectively).

According to URR values dialysis clearance was inadequate in 9 patients. However, only in 5 of them the Kt/V values also were <1.2. There was no significant difference between Kt/V, URR values and Hb level (r=0.138, p=0.510; r=0.082, p=0.717 respectively).

Table 1 - Characteristic of the study population.

Variable	Mean ± SD	Minimum	Maximum
Body mass index (kg/m^2)	17.45 ± 3.05	12.9	24.89
Hemoglobin (mg/dL)	8.49 ± 3.02	5.3	17.3
MCV (fL)	90.66 ± 10.95	60	118.5
MCHC (g/mL)	32.31 ± 0.72	31	33.9
Ferritin (ng/mL)	872.5 ± 878.2	65	4269
Iron (mcg/mL)	90.60 ± 54.24	25	225
Transferrin saturation (mg/dL)	33.92 ± 20.07	8.33	75
TIBC (mcg/mL)	278.32 ± 57.17	171	375
Unconjugated bilirubin (mg/dL)	0.61 ± 0.32	0.1	1.6
Reticulocyte count (%)	1.25 ± 0.90	0.3	4.2
LDH (IU/L)	444.65 ± 199.04	165	817
PTH (pg/mL)	872.5 ± 878	20	1110
Calcium (mg/dL)	8.06 ± 1.40	5.5	10.8
Phosphate (mg/dL)	5.76 ± 1.57	3.8	9.2
Alkaline phosphatase (IU/L)	812.76 ± 597.57	224	3050
Albumin (g/dL)	3.6 ± 0.66	2.7	4.8
Kt/V	1.62 ± 0.86	0.52	4.09
URR (%)	0.68 ± 0.13	0.34	0.94
EstNPCR (g/kg/day)	1.56 ± 0.07	0.61	3.29
rHuEPO dose (IU/kg/wk)	158.56 ± 83.82	66.44	342.85
Ferrous sulfate dose (IV) (mg/kg/wk)	4.05 ± 2.29	1.31	6.97
Ferrous sulfate dose (oral) (mg/kg/day)	2.09 ± 1.28	0.91	5.71

MCV - mean corpuscular volume, MCHC - mean cell hemoglobin concentration, TIBC - total iron binding capacity, LDH - lactate dehydrogenase, PTH - parathyroid hormone, URR - urea reduction rate, EstNPCR - Estimated normalized protein catabolic rate, rHuEPO - recombinant human erythropoietin.

There was no significant difference between URR values in patients with severe anemia and patients with mild to moderate anemia 8<Hb<11 (p=0.90).

Children with anemia were less likely to have a normal serum albumin. In 12 patients (48%) albumin was less than 3.5 g/dL. A significant relation was found between serum albumin and Hb level (r=0.511, p=0.01) (**Figure 2**). There was a significant difference between serum albumin values in anemic patients and patients without anemia (p=0.023). The mean albumin was 4.4 g/dL, 3.63 g/dL and 3.35 g/dL in patients with Hb>11, 8<Hb<11 and Hb<8 respectively (p=0.047). The EstNPCR was <0.8 g/kg/day in 6 patients (24%). No correlation was found between anemia and EstNPCR (r=-0.225, p=0.218). C-reactive protein was positive in 5 patients.

Intact PTH levels were more than 200 pg/mL in 16 patients (66%) and more than 400 pg/mL in 9 patients (37.5%). Finally, there was no statistically significant relation between iPTH level and Hb level (r=-0.205, p=0.336) but there was a reverse correlation between iPTH level >200 pg/ml and Hb level (r=-0.505, p=0.046) (**Figure 3**).

Discussion. The treatment of renal anemia poses major problem in children with ESRD. Only sparse information exists on the success of pediatric dialysis patients in reaching target hemoglobin levels. This report describes the status of a significant and treatable consequence of ESRD and anemia in hemodialysis patients.

The overall prevalence of anemia was higher (88%) in our study compared to the studies of Frankenfield et al[3] (37% in children aged 12–18 years), Fadrowski et al[7] (36.6%) and the 2001 North American Pediatric Renal Transplant Cooperative Study (63%).[8]

Fadrowski et al[7] revealed that increasing age and dialysis for less than 6 months were predictive of anemia. We did not find any correlation between age, gender and anemia but patients new to dialysis (treated for less than 6 months) were more anemic. The degree of anemia prior to the onset of dialysis may account for this finding but this could not be statistically assessed from the data set.

The recommended starting dosage of rHuEPO is 50-150 U/kg given 3 times weekly.[2] Our patients received a mean weekly rHuEPO doses of 158 U/kg compared to 208 U/kg in the study of Chavers et al.[2]

Some patients do not respond to rHuEPO therapy even if high doses are used. The main reason for EPO resistance is iron depletion or insufficient access to iron storage pools.[9] Almost all of our patients had iron supplements prescribed. In our study, only one patient had iron deficiency anemia. In contrast, in a

study conducted by Frankenfield et al,[3] 16% of anemic children and 5% of children with target hemoglobin were relatively iron deficient. However, there is no standards for iron adequacy in hemodialysis children, serum ferritin >40 ng/mL has been reported to be adequate in children on dialysis.[10] On the other hand, serum levels of ferritin, have been shown to be paradoxically high in ESRD patients with refractory anemia.[11,12] Increased ferritin production may prevent iron delivery to erythrocyte precursors.[11] Heavy iron overload (serum ferritin levels >800 ng/dL) was seen in nearly half of our patients.

Insufficient dialysis is associated with significant clinical morbidity, an increased risk of mortality, and likely contributes to anemia.[13,14] Frankenfield et al[3] showed that dialysis clearance no longer appeared to be an important factor accounting for the anemia in pediatric hemodialysis patients.[3] Similar to their finding, there was no correlation between dialysis clearance and hemoglobin level in the present study. Fistula access has been considered optimum for hemodialysis management.[15] In our study, 60% of patients have been dialyzed using AV fistula access and 25% of them had Kt/V values <1.2 and 81% of them were anemic. Whether the higher clearances achieved by using a fistula access would really affect anemia and other ESRD-related morbidity in children maintained on chronic hemodialysis has yet to be shown.

Severe secondary hyperparathyroidism appears to be important in the severity of anemia in children with chronic renal failure.[1] The PTH may be a direct inhibitor of endogenous EPO production.[16] Another mode of action of PTH in ESRD may be an increase in red blood cell osmotic fragility, leading to decreased red blood cell survival time in affected patients.[17] Synthetic PTH or serum from hyperparathyroid patients has been reported to inhibit red blood cell precursors in vitro in some studies.[18] Hyperparathyroidism may also affect anemia by causing bone marrow fibrosis, which reduces the available space for erythroid-forming units.[19] A serum intact PTH level >200 pg/mL has been shown previously to be strongly predictive of osteitis fibrosa in children.[20] The presence of severe hyperparathyroidism could adversely influence the response to EPO.[1] PTH effect on erythropoiesis can be overcome by higher doses of rHuEPO.[1] Severe hyperparathyroidism was seen in more than half of our patients, for that reason response to rHuEPO might be poor and requiring the use of much higher doses to reach a target hemoglobin level. Therapy to decrease the serum PTH concentration toward normal should be employed to attempt to improve the response to rHuEPO.

Low serum albumin and anemia were related in adult patients maintained on hemodialysis but in the context of inadequate dialysis clearance.[13] In our study, similar to that of Frankenfield et al,[3] anemia and albumin, were related independent of dialysis clearance in pediatric

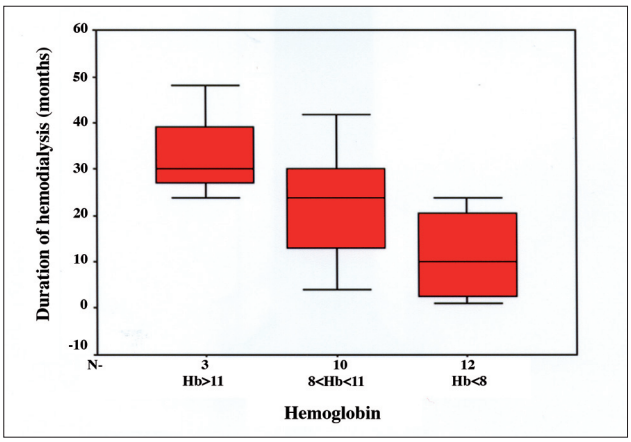

Figure 1 - The plot of duration of hemodialysis (months) in patients with target hemoglobin (Hb>11), mild to moderate anemia (8<Hb<11) and severe anemia (Hb<8).

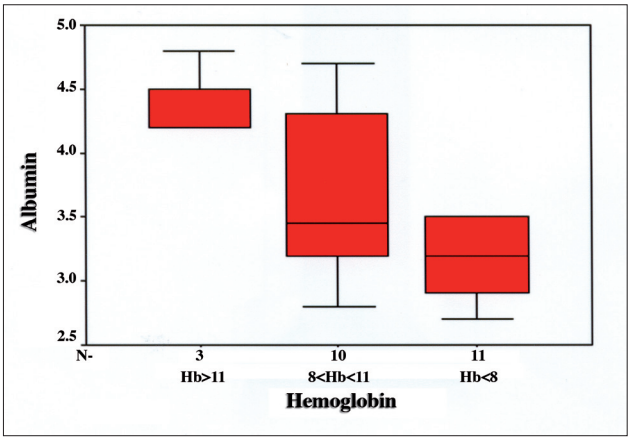

Figure 2 - The plot of albumin levels (g/dL) in patients with target hemoglobin (Hb>11), mild to moderate anemia (8<Hb<11) and severe anemia (Hb<8).

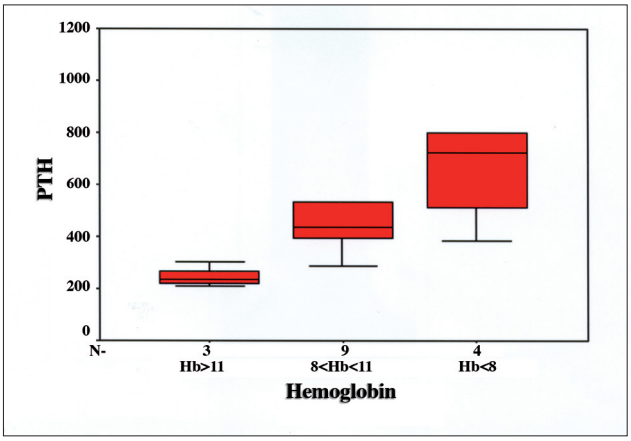

Figure 3 - The plot of serum intact parathyroid hormone levels >200 pg/mL in patients with target hemoglobin (Hb>11), mild to moderate anemia (8<Hb<11) and severe anemia (Hb<8).

patients and support the view that poor nutrition may be an additional factor for anemia. Improving nutritional state in dialysis patients may improve anemia and lead to a lower required EPO. In a meta-analysis by Hurot et al,[21] L-carnitine administrations, used to improve nutritional state, was associated with improved hemoglobin level, decreased EPO dose and EPO resistance in anemic dialysis patients.

Evidence of inflammation existed in 5 patients in our study. Refractory anemia appears to be more common in dialysis patients who also suffer from protein-energy malnutrition or inflammation.[22,23] Several previous studies reported an association between anemia and inflammation in dialysis patients, reflected by a high serum concentration of CRP.[23] Moreover, uptake of iron is lower than usual in inflammation.[24] The IL-6 and TNF-α has been shown to have a suppressive effect on EPO.[25] Finally, patients with inflammation may be more prone to gastrointestinal bleeding.[24]

In summary, pediatric chronic hemodialysis patients in Isfahan may be undertreated for anemia despite the extensive use of rHuEPO supplementation. We found this to be especially true for patients new on hemodialysis (less than 6 months) and with low serum albumin. Iron deficiency was not the main cause of anemia. Severe hyperparathyroidism, malnutrition and inflammation, should be considered as the other causes of anemia in this study. The results of this study indicate the need for continued improvement in the management of anemia in children undergoing chronic hemodialysis.

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