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Original Article

Post-transplant anemia in pediatric patients and its impact on patient and graft survival: single center experience

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Abstract

Introduction: Post-transplantation anemia (PTA) occurs frequently, with prevalence rates between 20 and 60% depending on the criteria used for defining anemia.
Aim of the work: We aimed to assess the prevalence of anemia after 6 months of transplantation in pediatric renal transplant patients under different protocols of immunosuppression, and to determine the impact of anemia upon long-term patient and graft survival.
Patients and methods: Based on the data of 108 renal transplants performed in our center, patients were categorized after 6 months according to their hemoglobin (Hb) levels into two groups. The first group with Hb more than 11gm/dl (group I, 29 cases) and the second group with Hb less than11gm/dl (group II, 79cases). We compared the two groups regarding post transplant complications (rejection episodes, hypertension, diabetes mellitus, infections, hepatic dysfunction, and patient and graft survival.
Results: we found no significant difference between the two groups regarding rejection episodes. However, the percentage of cases with chronic allograft nephropathy was significantly higher in the anemic group. The survivors with functioning grafts were significantly higher in cases with normal Hb. Moreover, living cases with graft failure were significantly higher in anemic group .Graft survival rate was better in the non anemic group. However, no difference in patient survival was detected. Also, we found no difference between the two groups regarding post-transplant complications.
Conclusions: From this study, we can conclude that the prevalence of post-transplant anemia is high pediatric renal transplant patients especially those receiving CNI and MMF, and it was associated with poorer graft outcome but no effect on patient survival .

Key words: Renal post-transplant anemia, long term outcome

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Introduction

Anemia has been implicated as an important risk factor for cardiovascular mortality in patients with CKD [1]. Post-transplantation anemia (PTA) occurs frequently, with prevalence rates between 20 and 60% depending on the criteria used for defining anemia [2,3].
PTA has been associated with an increased risk for congestive heart failure and left ventricular hypertrophy in kidney transplant recipients [4,5]. Given the high frequency of PTA and that cardiovascular disease is the leading cause of death

with a functioning renal allograft, persistent anemia may be an important contributor to mortality in this population [6].

The pathogenesis of posttransplant anemia (PTA) is multifactorial, but declining renal function and failing erythropoietin synthesis are suggested to play an important role [7]. Late post transplantation anemia (PTA) has been attributed to renal dysfunction, immunosuppressive drugs, antiviral agents, infections, blood loss, autoimmune hemolytic anemia, chronic inflammatory state and the use of angiotensin-converting enzyme inhibitors [8-10].

The three recent surveys enrolling the largest number of patients reported a prevalence of 30-40%. Severe anemia, requiring treatment based on current guidelines, is less frequent with prevalence rate of 10-15% [11-12].

Conflicting views had been published regarding the association between anemia and outcome in kidney-transplanted patients. No significant association was found between anemia and outcome (mortality or graft failure [13]. However, Heinze et al [14] suggested that anemia may be associated with mortality in the kidney-transplanted patients. The occurrence of PTA at 1 year is harmful to patient survival [15]**.** Moreover, anemia which is a treatable complication is significantly and independently associated with mortality and graft failure in kidney-transplanted patients [16]**.**

Anemia may also contribute to more rapid loss of renal function in patients with impaired renal function [17]. A recent study suggested that anemia significantly predicted the decline of renal function among CKD patients [18], and also among heart-transplant recipients [19]. Furthermore, Gouva et al [20] have recently shown that treating anemia in CKD patients can slow down the decline of renal function.

Aim of the work

We aimed to assess the prevalence of anemia after 6 months of transplantation in pediatric patients under different protocols of immunosuppression, and to determine the impact of anemia upon long-term patient and graft survival.

Material and methods

We included 108 pediatric renal transplant recipients (age $\leq$ 17 years) who received live donor kidney transplantation in our center in the period between 1983 and 2005. Most, if not all patients, who have undergone kidney transplantation in our center were anemic and spontaneous correction of anemia was noted and nearly completed within 4-6 months. They were categorized according to their hemoglobin (Hb) levels into two groups. The first group with Hb > 11gm/dl (group I, 29 cases) and the second group with Hb < 11gm/dl (group II, 79 cases). Both groups were matched regarding previous blood transfusion.

Methods: Clinical data were reviewed. Demographic data included recipient age and gender; donor age and gender; causes of end-stage renal disease; and HLA-A, B, & DR mismatching. All recipients were regularly followed up (with mean follow period 120±12 months). The follow up visits were frequent early post-transplantation and then gradually spaced. Each visit, the graft function was assessed by serum creatinine, creatinine clearance and urine analysis; in addition to other laboratory investigations including complete blood picture, immunosuppressive drug levels. All recipients were closely and regularly followed up for evaluation of medical or surgical complications. Abdominal and Doppler ultrasound were also performed.

Immunosuppression: Prednisolone was started on the day (-1) of transplantation at a dose of 8.5 mg / kg and reduced gradually till the smallest dose of 0.15 mg / kg/day by the end of the 9^{th} month. Azathioprine (Aza) was given in a dose of 3 mg/kg/day for old regimen (steroid and aza) and in a dose of 1.5 mg /kg /day in group of steroid, Aza, and Cyclosporine (CsA). Only CsA was given 2-3 days pretransplantation. CsA was introduced in a dose of 8.5 mg/kg and it was adjusted to keep the trough level 200-250 ng/ml in the first month, 150-200 ng/ml in the second month and 100-150 ng/ml thereafter. Antibody induction therapy was given to the majority of cases according to our policy. Antibody induction therapy –using basilixmab 20mg at days 0 and 4 –was added from the late nineties till now. CsA trough level was measured at first using Radio-immune Assay Kits, (Sandoz, Basel, Switzerland), and then using monoclonal specific antibody, (Abbott laboratories, Abbott Park, IL).

Tacrolimus therapy was given at a dosage of 0.1mg/kg/day and the dose was adjusted to achieve target whole-blood trough concentrations of 10-15ng/ml during the first 2 weeks then 5-10 ng/ml thereafter. Tacrolimus concentrations in whole blood were measured by the IMx analyzer (Abbott laboratories, Abbott Park, IL). Mycophenolate Mofetil (MMF) was administered in a dose of 20-30mg/kg twice daily.

Graft biopsy was performed if there was any

clinical suspicion of rejection (unexplained rise of serum creatinine more than 25 % of the basal level). Before 1994, we were defining acute rejection into 3 grades: mild, moderate and severe according to the degree of cellular infiltration in the graft. After 1994, we followed the Banff classification with its modifications (acute and chronic allograft nephropathy).

All acute rejection episodes were biopsy proven and treated by 10 mg /kg/ day methyl prednisolone for 5 days. Steroid–resistant rejection was treated by anti-thymocyte globulin. Plasmapheresis was added as an adjuvant therapy in cases of accelerated or vascular rejections.

Statistical analysis: Statistical analysis was carried out using IBM-compatible SPSS for windows version 11.5 (SPSS Inc., Chicago, IL). For comparison of continuous data, the T-test was utilized. Chi-square test was employed for comparison of simple proportions. Patient and graft survival were computed using Kaplan-Meier technique. Differences in survival were calculated by the log-rank test. P value of less than 0.05 was considered statistically significant.

Results

Table (1) illustrated the donors and recipients characteristics. Majority of recipients were males in their second decade of life while nearly half of the donors were females in their third decade of life. The two groups were homogenous in terms of donor's age, sex; recipient age, prior blood transfusion and pre-transplant hypertension. In addition, no preformed antibodies against donor antigens were detected in the pre-transplant cross-match of any of the study patients. The techniques employed for re-establishment of urinary continuity were also essentially similar. The two groups were matched regarding the type of primary immunosuppression protocols with the majority being on steroid, CsA and aza.

Rejection episodes: No significant difference was found between the anemic and non-anemic groups regarding either those who experienced single rejection episode (p= 0.079); repeated rejections (p=0.58); cases with acute cellular rejection (p=0.95), acute vascular rejection (p=0.86) or chronic rejection (p=0.19). However, on dealing with anemic patients alone, we observed that the number of cases with chronic allograft rejection was significantly higher among severely anemic patients (p=0.025, table 2).

Outcome: At the last follow up, the survivors with functioning grafts were significantly higher in cases with normal Hb (p=0.013). However, living cases with graft failure were significantly higher in anemic group (p=0.023, table 3). Graft survival rates were 98.3% in normal group vs.97.4 % in anemic group at 1-year; 98.1% vs. 96.1% at 5-year; and 93.9% vs. 82.2% at 10-year respectively (figure 1, p< 0.001). The corresponding patient survival rates were 100% vs. 98.7% at 1-year; 100% vs. 98.7% at 5-year; and 100% vs.98.7% at 10-year respectively (figure 2, p=0.099).

Graft function: In spite of comparable results of graft function in both groups at one year (p>0.05), the percentage of cases with serum creatinine less than 1.5mg/dl, was significantly higher in group I (p=0.016), while the percentage of cases with serum creatinine more than 3 mg/dl, was significantly higher in group II at the last follow up (p=0.01, table 4). However, both groups were matched regarding cases with normal graft function at the last follow up.

Complications: The two groups were comparable regarding post-transplant complications especially diabetes mellitus; serious bacterial infections, hepatic problems and hypertension (p>0.05, table 5). Two cases (2.6%) died mostly due to cardiovascular causes in anemic group while no mortality was reported among patients of the other group. Moreover, no single case of malignancy was reported.

Table 1: Characteristics of donors and recipients among patients of the two groups

	Group (I) Normal Hb N=29	*Group (II) Anemic group N=79*	*p value*
Mean age of donors (years)	34.1±9.7	36.5±10	0.24
Donor sex (male/female)	10/19	34/45	0.42
Mean age of recipients (years)	15.07±2.4	13.9±3.3	0.39
Recipient sex (male/female)*	20/9	55/24	0.94
Original kidney disease:			
-Immunological causes	6	10	0.24
-Non- immunological causes	23	69	

Pretransplant hypertension	12	36	0.69
Pretransplant blood transfusion	15	39	0.89
Pretransplant dialysis	23	75	0.67
HLA type I ≥ 50 %match	26	72	0.87
type II 50% match	26	75	0.32
Type of immunosuppression			
-CNI-free	2	1	0.35
-CsA-based	25	69	0.87
-Tac-based	2	9	0.43

* Only significant variable with multivariate analysis

Table 2. Rejection episodes in both groups

	Group (I) Normal Hb N=29	*Group (II) Anemic group N=79*	*p value*
One rejection	7	21	0.79
≥ 2 rejections	3	4	0.58
Type of rejections			
-Acute vascular	0	2	0.95
-Acute cellular	10	24	0.86
-Chronic allograft nephropathy	3	19	0.19

Rejection episodes in anemic patients

	Mild anemia N=25	*Moderate anemia N=21*	*Severe anemia N=33*	*p value*
One rejection	8	2	21	0.29
≥ 2 rejections	1	2	1	0.29
Type of rejections				
-Acute vascular	2	0	0	0.17
-Acute cellular	6	5	13	0.17
-Chronic allograft nephropathy	3	3	13	0.025

Table 3. Condition at last follow up of patients who continued primary immunosuppression

	Group (I) Normal Hb N=29	*Group (II) Anemic group N=79*	*p value*
Live +function graft	28 (96.6%)	57 (72.2%)	0.013
live+ dialysis	1 (3.4%)	20 (25.3%)	0.023
Died+ function graft	0	1 (1.3%)	0.056
Died+ failed graft	0	1 (1.3%)	0.056

Table 4. Clinical grading of anemic vs. non anemic patients (basal and at the last follows up)

	Group (I) Normal Hb N=29	*Group (II) Anemic group N=79*	*p value*
At one year			
Grade 1 cr* <1.5 mg/dl	24 (82.8%)	70 (88.6%)	0.63
Grade 2 cr 1.5---3 mg/dl	5 (17.2%)	8 (10.1%)	0.5
Grade 3 cr > 3 mg/dl	0	1 (1.3%)	0.59
Last follow up			
Grade 1 cr <1.5 mg/dl	6 (20.75%)	19 (24.1%)	0.71
Grade 2 cr 1.5---3 mg/dl	20 (69%)	32 (40.5%)	0.016
Grade 3 cr 3—5 mg/dl	3 (10.3%)	28 (35.3%)	0.01

*Serum creatinine

Table 5. Types of serious complications encountered among the two groups

	Group (I) Normal Hb N=29	*Group (II) Anemic group N=79*	*p value*
Malignancies	0	0	
Hepatic impairment	2 (6.9%)	1 (1.3%)	0.35
Post-transplant Hypertension	18(62.1%)	48 (60.8%)	0.92
Posttx diabetes mellitus	1 (3.4%)	1 (1.3%)	0.95
Bacterial infections	1 (3.4%)	7 (8.9%)	0.59

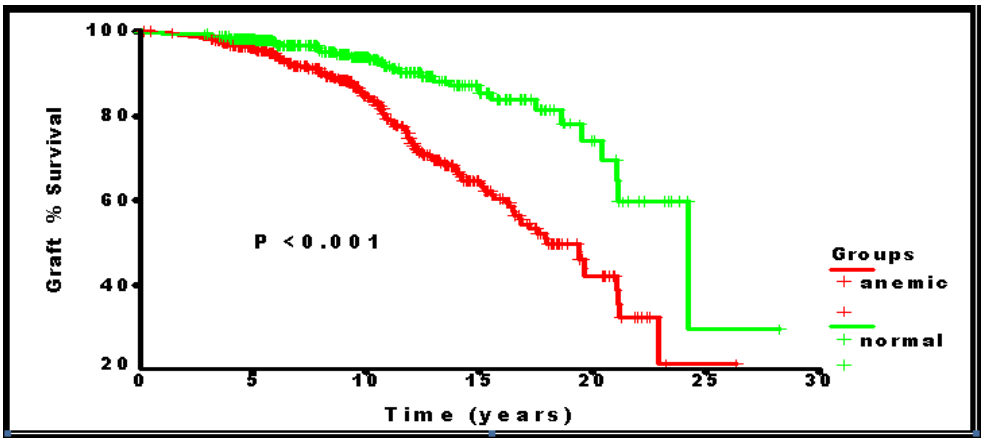

Fig. 1. Graft survival in anemic and cases with normal hemoglobin.

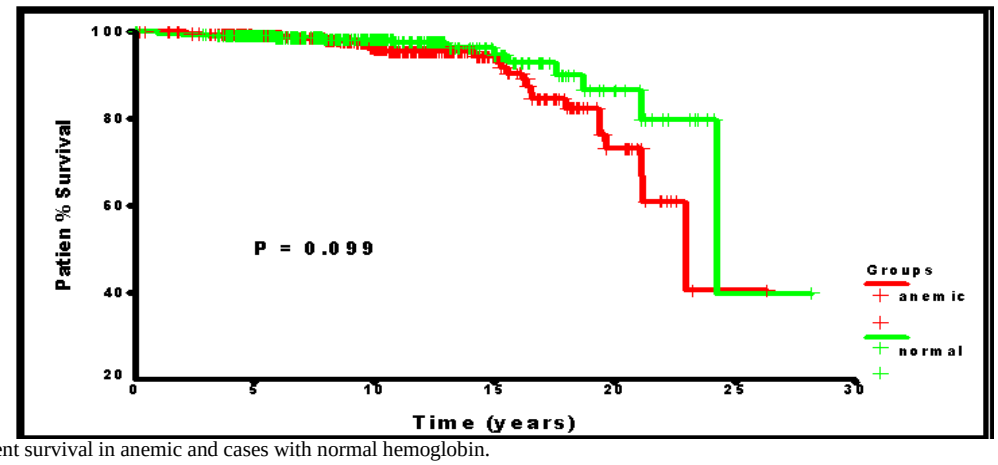

Fig. 2. Patient survival in anemic and cases with normal hemoglobin.

Discussion

Anemia in pre-transplant patients usually is a result of erythropoietin (EPO) deficiency, resistance to EPO, iron deficiency (either absolute or functional), and/or blood loss [21-24].

It is reported that anemia is a common problem in kidney transplant recipients and it is an independent risk factor for post transplant left ventricular hypertrophy and cardiovascular diseases [25-27]. The incidence of cardiovascular events (myocardial infarction, cardiovascular death, angina, congestive heart failure) is 35%, less likely in the first six months after transplantation in diabetic transplant recipients with hematocrit 30% compared to those with lower hematocrit levels [23].

Out of 108 pediatric renal transplant recipients enrolled in this study, we found that anemic patients (according to WHO classification of anemia) represented 53.7% (31.6% were mildly anemic, 26.5% were moderately anemic and 41.7 % were markedly anemic). These results were higher than that reported by large multi-institutional studies which reported lower prevalence of anemia 30–40% at various times after transplantation [24] and 38.6% in another European study from 72 European centers of kidney transplant recipients [11]. Moreover, the prevalence of severe anemia was 8.5% compared to 41.7 % in the present study.

However, shah et al [8] reported that there is a high prevalence of anemia among transplant population, in 45% of cases. The high prevalence of PTA cannot be attributed to uncorrected pretransplant anemia of CKD [29].

This coincides with our suggestion that although most of our patients were anemic at the time of transplantation, yet this factor alone can not be implicated as a sole factor in genesis of post-transplant anemia. Anemia among our patients might be explained by multiple factors: female gender; calcineurin inhibitors, azathioprine, mycophenolate mofetil, poor graft function, acute rejection episodes, recent infection, and the use of ACE inhibitors and angiotensin II receptor blockers [30]. Patients who were receiving CsA based protocols were associated with lower Hb levels especially if associated with MMF or azathioprine which could be explained by their negative effect on the bone marrow [31] which was matched with findings of Yorgin et al 2002 Who reported that cyclosporine use was associated with lower Hb levels, an observation previously described in children [32]. Multivariate analysis of the previous factors showed that only the recipient's sex plays independently among our patients.

In an Egyptian survey [33], they found that 47% of Egyptian healthy adolescent girls and boys were anemic which decreased to 30 % by the year 2000. Poor eating habits are the main reason for the high rates of anemia among adolescents in Egypt.

The high prevalence of posttransplant anemia cannot be attributed to uncorrected pretransplant anemia of CKD as the prevalence at five years after kidney transplantation ranges from 30–35% in recipients with functioning allograft [25].

The antiproliferative agent, azathioprine, is well known to cause bone marrow depression, and despite a different mechanism of action, MMF was observed to cause similar levels of anemia [28]. MMF use had demonstrable association with anemia especially when combined with CsA which was matched with findings of others [29]. Cyclosporine use was associated with lower Hb levels, an observation previously described in children [30].

At the last follow up, we observed that the survivors with functioning grafts were significantly higher in cases of group I ($p=0.013$). However, living cases with graft failure (25.3%) were significantly higher in group II ($p=0.023$). Along the whole period of follow up, graft survival rates were significantly higher in group I ($p< 0.001$), however, the corresponding patient survival rates were comparable in both groups ($p=0.099$).

Regarding graft survival, our results were matched with that reported by Molnar et al [16] who showed that, in a single center Hungarian study of 938 kidney transplant recipients, the long term effects of anemia on patient and graft survival. During a follow-up of approximately 4 years, 79 patients (8.4%) returned to dialysis and 118 patients (12.6%) died with 30% of deaths resulting from infection, 23% from cardiovascular disease, and 18% from malignancy. In spite of heterogeneity of immunosuppression, they concluded that anemia predicted graft failure and mortality, independently of estimated glomerular filtration rate, age, gender, time on dialysis, and other co-morbidities. Similarly, Chhabra et al [31] showed that PTA was associated with worse patient and graft survival. Molnar et al [16] demonstrated that the presence of anemia was associated with poor survival and graft failure in kidney transplant recipients with 1.69 times higher chance to die within 4 years; and 2.46 times higher chance to return to dialysis during the same follow-up period than patients without anemia. Regarding patient survival, our results were matched with the results of Winkelmayer et al [32] who did not find significant association between mortality and serum Hb.

Cases with acute cellular rejection were higher in the anemic group but this did not rank to statistical significance (p=0.06). A finding which was matched with that reported by Chhabra et al [30] who showed that PTA was associated with higher rates of acute rejection when compared with non-anemic recipients.

However, the percentage of cases with chronic allograft nephropathy was significantly higher in the anemic group (p= 0.001). The commonest cause of allograft loss is death of patients with functioning allograft (mostly due to cardiovascular events). Moreover, cardiovascular risk factors are also very relevant to the second most common cause of allograft loss (chronic allograft nephropathy) [33,5]. Similar to the CKD population, cardiovascular co-morbidities are the leading causes of death in kidney transplant patients [34]. Anemia lead to hyperkinetic circulation, thicker left ventricular wall and congestive heart failure in kidney transplant patients. These factors were independent predictors of mortality in transplant population [19].

Our study has demonstrated that cases with graft failure increased significantly with advancement of anemia. This also was matched with that reported by Molnar et al [31] as they showed that each 1 g/L decrement in the level of serum hemoglobin increased the odd ratio of graft failure by 1.9% during the 46 months follow-up period.

In spite of comparable results of graft function in both groups at one year (p>0.05), by time the percentage of cases with normal graft function was significantly higher in the non anemic group (p=0.001), while the percentage of cases with graft dysfunction was significantly higher in the anemic group at the last follow up (p=0.001).

Several studies suggested that treating anemia can slow down the decline of renal function in patients with chronic kidney failure [35]. It was also notable that chronic hypoxia and oxidative stress are profibrogenic stimuli for tubular cells and interstitial fibroblasts, eventually representing a common pathway to the progression to ESRD. In transplant recipients, the hypoxic damage might be potentiated by the use of immunosuppressive agents, particularly calcineurin inhibitors, and by the concomitant presence of congestive heart failure, which reduces renal blood flow [19].

Conclusions: From this study, we can conclude that the prevalence of post-transplant anemia is high in pediatric renal transplant patients especially those receiving CNI and MMF, and it was associated with poorer graft outcome but no effect on patient survival.

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