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Post-Transplant Erythrocytosis in Live Donor Kidney Transplant Recipients: A Retrospective Single Center Study

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ABSTRACT

Introduction

Post-transplant erythrocytosis (PTE) is defined as persistently elevated hemoglobin>17 g/dl and/or PCV>51% in kidney transplant recipients. The incidence of PTE varies from 5% to 17%, with occasional life-threatening thromboembolic complications. We aimed to study the prevalence, risk factors and complications of PTE.

Methods

We conducted a retrospective single center study in 132 kidney transplant recipients who had undergone live donor kidney transplantation at Tribhuvan University Teaching Hospital, Nepal, between October 2017 and March 2019. Prior approval was obtained from Institutional Review Committee of Institute of Medicine. Patients with hemoglobin>17 g/dl were defined as PTE group, and others as non-PTE group. The pattern of hemoglobin, serum creatinine, pre-transplant hemoglobin, native kidney disease, immunosuppression medications, rejection episodes, and new onset diabetes after transplantation were analyzed and compared between two groups.

Results

Out of the 132 kidney transplant recipients, PTE was diagnosed in 28 (21.2%) patients, out of which 27 patients (96.4%) were male and 1 (3.6%) were female with the mean time of onset at 7 months after transplantation. Patients with erythrocytosis had a relatively shorter duration of pre transplant dialysis (p=0.001). The mean pre transplant Hb and Hct in PTE group was 9.72g/dl and 30.35% whereas in non PTE group 10.02 g/dl and 31.31%. Thromboembolic and any other PTE related complications were not observed. Seventeen patients of PTE (60.7%) were treated with ACE Inhibitors and 11 (39.9%) patients did not require any treatment.

Conclusion

Post-transplant erythrocytosis was seen in nearly one fifth kidney transplant recipients at mean time of seven months post-transplantation; was more common in male with good graft function, and short duration of pre transplant dialysis. Response to ACE inhibitors was good.

Keywords

Erythrocytosis, recipient, renal transplant

INTRODUCTION

Anemia of multifactorial etiology is prevalent in patients of chronic kidney disease (CKD). There are two major factors which contribute to the correction of anemia after kidney transplantation: adequate production of erythropoietin by the transplanted graft; and elimination of bone marrow inhibitors attending the uremic syndrome.[1,2] After the kidney transplantation, erythropoietin secretion peaks within 3 days, reticulocytosis begins at about 1 week, and correction of anemia is anticipated over 3 months. Thereafter, erythropoietin levels decline in a negative feedback fashion over the next 4 to 8 months toward normal levels.[3-5] The type of immunosuppression, the level of graft function, and the occurrence of acute rejection appear to influence the rate of correction of renal anemia and the level of hematocrit attained.

Post-transplant erythrocytosis (PTE) was first recognized by Nies et al. in kidney transplant recipients in 1965.[6] PTE occurs in 5-17% of kidney transplant recipients.[7] PTE is usually benign and transient, but may follow a more protracted course and in some instances, may cause thromboembolic complications. PTE is defined by the American Society of Transplantation as persistently elevated hemoglobin (Hb) >17 g/dl and or hematocrit >51% in kidney transplant recipients. The etiology of PTE is not fully understood, but it probably results from an over production of erythropoietin (EPO) by the kidney allograft or by native kidney. It may also be caused by an unusually exaggerated response of the bone marrow to normal levels of erythropoietin.[8] The important risk factors for PTE include male gender, preserved glomerular filtration rate, and retained native kidneys.[9] Other risk factors include transplant renal artery stenosis (TRAS), hydronephrosis, low erythropoietin (EPO) requirement, high pre-transplant Hb, autosomal dominant polycystic disease, short duration of maintenance dialysis on pre transplant, diabetes, smoking, immunosuppressive medications especially cyclosporine and rejection-free graft.[9,10]

PTE has an important impact on blood rheology. Patients with PTE may experience malaise, headache, plethora, lethargy and dizziness. Thromboembolic event is the most serious complication and has been reported in 10 to 30% cases.[11] There are numbers of treatment modalities are available for the management of PTE. These include phlebotomies, angiotensin converting enzyme Inhibitors, theophylline and native kidney nephrectomies.[12-14] The aim of this study was to determine the prevalence and timeline of development of PTE in live donor kidney transplant recipients, to identify the factors associated with development of PTE by comparing several variables in the PTE and non PTE patients, to document the complications arising due to PTE and its response to management.

METHODS

This retrospective study was conducted on patients who had undergone live donor kidney transplantation at Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal and were being followed in the outpatient department on a regular basis. Prior approval was obtained from the Institutional Review Committee (IRC) of Institute of Medicine. All patients transplanted between October 2017 and March 2019 and who had at least 12 months of follow up were included in the study. PTE was diagnosed when patients Hb was ≥17 g/dl and or PCV ≥51% irrespective of gender.

Clinical data were retrieved from the case notes on a pre-designed porforma. These included: pre-transplant Hb, native kidney disease, duration on dialysis, native kidney nephrectomy (if applicable), immunosuppression medications, rejection episodes, graft biopsy findings and new onset diabetes after transplantation (NODAT). Similarly, post-transplant complete blood counts, graft function, urine analysis, complications related to PTE and management of PTE and complications, if any, were noted. Data was recorded in Excel sheet.

Those patients with estimated glomerular filtration rate <30 ml/min, transplanted within 6 months and obstructive airway diseases causing erythrocytosis and those with missing information or follow up were excluded from the study. Retrospective nature of the study exempted the need to take informed consent from the participants.

Hemoglobin and hematocrit of the 7th post-transplant day, 1 month post-transplant, 6 months post-transplant, 9 months, at the onset of PTE, and 1 year post transplant were recorded. Those patients with Hb level ≥17 g/dl (PTE group) were compared with patients who had normal hematocrit (non-PTE group).

Statistical analysis was done with Medcalc statistical software Ver. 12.7.0.0 and online statistical calculator (http://www.socscistatistics. com/). Data were presented as mean, median, standard deviation. Test of significance was done by Chi-square test (2 × 2, 5 × 5 contingency table) for categorical variables and t-test/ANOVA test for continuous variables between those who developed PTE and those who did not develop PTE. The level of significance was taken as < 0.05.

RESULTS

There were 132 kidney transplantations performed during the study period who met inclusion criteria. Of those, 28 developed PTE (HCT>51%) making a prevalence of 21.2%. Table 1 summarizes the

Table 1. Baseline characteristics of Post-transplant erythrocytosis and nonposttransplant erythrocytosis

Characteristics	PTE group (n=28), n(%)	non PTE group (n=104),	p value
Mean age (years)	33.25	36.23	0.08
Gender			
Male	27 (96.4%)	85 (81.7%)	0.05
Female	1 (3.57%)	19 (18.2%)	
Native kidney disease			
CGN	23 (82.1%)	66 (63.4%)	
DKD	0	14 (13.4%)	
Obstructive Uropathy	0	4 (3.8%)	
IGAN	2 (7.1%)	9 (8.6%)	
ADPKD	0	3 (2.8%)	
FSGS	0	2 (1.9%)	
MPGN	2 (7.1%)	2 (1.9%)	
VUR	0	1 (0.9%)	
Lupus nephritis	0	3 (2.8%)	
Alport syndrome	1(3.5%)	1 (0.9%)	
Immunosuppressive agent			
Tacrolimus	28	104	
Mycophenolate mofetil	28	104	
Steroid	28	104	
Pre transplant Hb (g/dl)	9.72	10.02	0.22
Pre transplant Hct (%)	30.35	31.31	0.21
NODAT	0	2 (1.9%)	
Duration Of HD (Months)	10.45	17.82	0.001
HTN	15 (53.5%)	46 (44.2%)	0.38
Rejection	2 (7.1%)	5 (4.8%)	0.62
Peak Hb (g/dl)	18.42	14.88	0.002
Peak Hct (%)	56.22	46.05	0.001

HD, hemodialysis; NODAT, new onset diabetes after transplant; HTN, hypertension; Hb, hemoglobin; CGN, chronic glomerulonephritis; DKD, diabetic kidney disease; IGAN, IgA nephropathy; ADPKD, adult dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; VUR, vesicoureteric reflux.

demographic, clinical and laboratory parameters of two groups. There were 96.4% male in PTE group and 81.7% male in non PTE group. Out of total of 28 patients with PTE, 27 patients (96.4%) were male and 1 (3.6%) were female, though overall these differences were not statistically significant (p=0.05). PTE was seen in younger age group as compared to non PTE group (mean age in years 33.25 vs 36.23 respectively) but not statistically significant (p=0.08). Patients with erythrocytosis had a relatively shorter duration of pre transplant dialysis (P=0.001). The groups were otherwise very similar as regards with native kidney disease and type of antihypertensive medications.

Almost all patients in the two groups were on triple immunosuppression with tacrolimus, mycophenolate mofetil and oral steroid. The mean time of onset of PTE was 7.07±2.9 months after transplantation. PTE was diagnosed as early as 1 month post-transplant in three patients. Peak Hb and Hct in PTE group was 18.42g/dl and 56.22% respectively and in non PTE group 14.88g/dl and

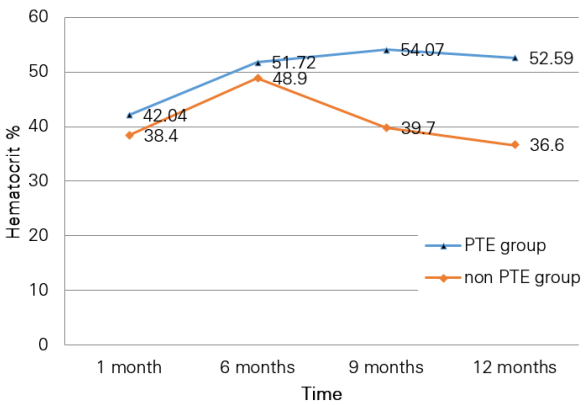

Fig 1. Evolution of hematocrit in relation to duration after transplantation.

Table 2. Laboratory data of patients with post-transplant erythrocytosis, PTE (n=28)

Characteristics	Hb (g/dl)	HCT (%)	Creatinine (umol/L)
7th post-transplant day	9.26	29.44	126.75
1 month post-transplant	13.28	42.04	114.35
6 months post-transplant	16.92	51.72	106.23
9 months post-transplant	17.72	54.07	108.34
At onset of PTE	17.82	54.61	101.92
12 months post-transplant	17.28	52.59	103.35

46.05% respectively. The mean pre transplant Hb and Hct in PTE group was 9.72g/dl and 30.35% whereas in non PTE group 10.02g/dl and 31.31% which was not statistically significant (p=0.22 and 0.210 respectively). Average level of Hb and Hct at onset of PTE was 17.82 g/dl and 54.61% respectively. Renal functions were significantly better at the onset of PTE in the same group, with mean serum creatinine being 101.92 umol/L. PTE group maintained excellent graft function till their last follow up.

In PTE group none of the patients developed NODAT whereas in non PTE group 2 patients (1.9%) developed NODAT. Hypertension was present in 53.5% of the patients in PTE group compared with only 44.2 % of the patients in non PTE group (p=0.38). Documented graft rejection was present in 7.1% of the PTE group against 4.8% of the patients in non PTE group, though it was not statistically significant (p=0.62).

Table 2 shows mean hemoglobin and hematocrit values of patients with PTE against serum creatinine at different time lines post transplantation. Figure 1 graphically depicts the hematocrit values in PTE vs non PTE groups at different timelines after transplantation.

None of the patients in PTE group experienced malaise, headache, lethargy or dizziness. Similarly, thromboembolic event was not observed and hydronephrosis or transplant renal artery stenosis was not seen in any patients with PTE group.

Seventeen (60.7%) of PTE patients were treated with ACE inhibitors and 11 (39.9%) patients did not require any treatment. None of the patients in PTE group underwent phlebotomy or native kidney nephrectomies.

DISCUSSION

PTE is a frequent unnotified complication in the post-transplant period and does not generally have significant impact on graft function.

The pathogenesis of post-transplant erythrocytosis is affected by various factors such as the absolute or relative rise of EPO, increased sensitivity of erythroid precursors for EPO mediated by the increase in IGF-1, IGF-1 Binding Protein,[16] and absent uremic toxins. Angiotensin-II (AT-II) activates erythroid progenitors directly and or indirectly by direct EPO release to increase EPO production. Angiotensin-converting enzyme (ACE) increases erythropoiesis by metabolizing N-acetyl-seryl-aspartyl-lysyl-proline which is a natural inhibitor of erythroid progenitors.[14,17]

In the present study PTE was observed in 21.2% of post-transplant recipients, which is slightly higher prevalence compared to other studies.[7] Patients with erythrocytosis were mostly male (27 male, 96.4% vs 1 female, 3.6%) (Table 1), which is in agreement with other studies showing that PTE is more common in males.[18] The most definitive risk factor for PTE is good graft function which is shown in all observations.[9,19] In our study, all the patients maintaining good graft function (mean creatinine = 101.92 umol/L) during the onset of PTE. Native kidney disease, age and gender, pre-transplant Hb and immunosuppression medications did not have any impact on the PTE occurrence in our study. In our study, patients with PTE seemed to have a higher value of acute rejection episodes (7.1% vs 4.8%), which is rather unexpected and contrary to most previous studies showing that PTE occurs in those who had rejection free course before developing erythrocytosis. However, it was statistically not significant and could have been due to the small sample size (Table 1).

The result of influence of immunosuppressive therapy on occurrence of PTE could not be assessed as both the group received same immunosuppressive therapy. None of the patients in PTE group develops NODAT whereas 2 (1.9%) patients out of 104 patients in non PTE group developed NODAT. In our study, the mean time of onset of PTE was 7.07 (SD ± 2.9) months after transplantation, which is comparable to other studies also.[20] High blood pressure was present in 53.5% of the patients with PTE and needed antihypertensive medications where as 44.2% of patient in non PTE group were on antihypertensive medications. This finding is in agreement with the proposition that erythrocytosis increases blood pressure by increasing the blood volume and viscosity that increases vascular resistance leading to worsening of hypertension.[10]

The other suggested factors affecting PTE include native kidney disease, the duration on dialysis and transplant renal artery stenosis.[9,10] In our study among these factors, short duration on dialysis prior to transplant was the only factor which was found to be significantly associated with post-transplant erythrocytosis (Table.1) We did not encounter any case with transplant renal artery stenosis.

Symptoms of PTE occur because of increased

viscosity and increased blood volume which include headache, tinnitus, hypertension, fatigue, blurring of vision, and thromboembolic episodes.[10] None of PTE patients in our study had symptoms related to PTE including any thromboembolic complications; all the patients maintained good renal functions during the follow up. (Table.2) Kidney disease improving global outcomes recommends starting treatment when Hb >17 g/dl or PCV >51%. A number of therapies are available for the management of PTE. When hematocrit values exceed 55% therapeutic phlebotomy is required to maintain hematocrit around 50% to minimize the risk of thromboembolic events.[11] However a more conservative medical treatment suffices at a lower hematocrit level. RAS (renin angiotensin system) inactivation by ACE inhibitors and angiotensin receptor blocker (ARB).[13,14] Blockade of renal A2 adenosine receptor by theophylline has been shown to reduce erythropoietin secretion.[21] In our study, 17 patients (60.7%) were treated with ACE inhibitors and remaining 11 (39.2%) patients did not receive any treatments.

Some of the limitation of our study are: small sample size, retrospective design, single center, only live donor kidney transplant recipients and unavailability of erythropoietin (EPO) level. However, well planned analysis of the available information serves as baseline and incites future research in this field.

CONCLUSION

Post-transplant erythrocytosis was observed in nearly one fifth kidney transplant recipients, a prevalence slightly higher than reported from elsewhere. It was seen at around 7 months post-transplant with good graft function and shorter duration of pre-transplant dialysis. Any symptoms or complication related to PTE were not observed; more than half of the PTE patients were prescribed ACE inhibitors and responded well.

CONFLICT OF INTEREST

None declared.

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