Evaluation of contributing factors of post transplant erythrocytosis in renal transplant patients

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Abstract

Objective: To evaluate the prevalence and contributing factors causing post transplant erythrocytosis in renal transplant patients.

Methods: This retrospective study was conducted on live related renal transplant patients at SIUT. The records of all transplant recipients transplanted between April 2008 and December 2008 and who had at least 24 months follow up were studied. Patients in whom haematocrit exceeded 51% and those who received treatment for it were classified into post transplant erythrocytosis group.

Results: Out of 200 renal transplant patients who had functioning graft at the time of analysis, 40 (20%) developed post transplant erythrocytosis (HCT ≥51%) after a mean interval of 9.5± 2.5 months. Patients with erythrocytosis were mostly males (95% in PTE group vs 73.75% in non PTE group) ,had a shorter period on dialysis before undergoing renal transplantation (9.28 months in PTE group vs 14.56 months in non PTE group) and had relatively better graft function at the onset of erythrocytosis as judged by serum creatinine (S. Creatinine of 1.06±0.29mg/dl in PTE group vs 1.37± 0.51 mg/dl in non PTE group). No thrombotic complications were observed. All patients with erythrocytosis were treated with enalapril (ACE inhibitors) and 28 out of 40 required phlebotomy in addition to ACE inhibitors. The mean HCT at the time of last follow up in treated patients was 48.61±1.85%.

Conclusion: Post transplant erythrocytosis generally occurs in male patients with good graft function, thrombotic complications are of rare occurrence and response to ACE inhibitors is good.

Keywords: Transplant, Erythrocytosis, Thrombosis. (JPMA 62: 1326; 2012)

Introduction

Post transplant erythrocytosis (PTE) is defined as persistently elevated haematocrit (Hct) above 51%. Among renal allograft recipients post transplant erythrocytosis is a frequent phenomenon occurring in 10 to 20% of the recipients. It is usually encountered within 8 to 24 months of post renal transplant period.[1] PTE is often a benign phenomenon and temporary in its course, it remits on its own but HCT may remain elevated for years.[1] It may sometimes be associated with thromboembolic phenomenon.[1]

The etiology of PTE is poorly understood. A number of contributing factors have been linked to PTE including acute and chronic rejections, transplant renal artery stenosis, smoking, diabetes, type and dose of immunosuppression, use of diuretics, anti hypertensive medication, extent of allograft function and duration on dialysis.[1-3] It is more common in the male gender. Although smoking is not believed to be an essential factor, it is considered to be an important one.[4] Some studies have revealed relation between drug consumption especially corticosteroids and PTE,[5] while others have noted that the prevalence of erythrocytosis is higher in patients receiving cyclosporine based immunosuppression.[6]

The pathologic elevation of haematocrit has a substantial impact on blood rheology and just as in other forms of erythrocytosis, 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 and can be fatal.[7] A number of treatment modalities are available for the management of PTE. These include phlebotomies, angiotensin converting enzyme inhibitors, theophyllins and native kidney nephrectomies.[8-10]

The purpose of this study was to evaluate the contributing factors causing PTE in post renal transplant patients by comparing several variables in the PTE and non PTE patients.

Patients and Methods

This retrospective study was conducted on patients who had undergone live related renal transplant at Sindh Institute of Urology and Transplantation (SIUT) and were being followed in the out patient department on a regular

basis.All patients transplanted between April 2008 and December 2008 and who had atleast 24 months of follow up were included in the study. Clinical data and lab results were retrieved from the case notes on a specially designed performa. Patients who lost their graft before 24 months, and those with missing information or follow up were excluded. Patients who had known pulmonary disease causing erythrocytosis were also excluded.

Complete blood count was checked by autoanalyser sysmex machine Erythocytosis was defined as HCTof ≥51% for both gender. Those who developed erythrocytosis were compared with patients who had haematocrit value below 51%.The study variables included age, gender, primary renal disease, smoking habits, immunosuppression regime, anti hypertensive medications, duration on dialysis, blood transfusions during dialysis, acute rejections. Haemoglobin, haematocrit and serum creatinine were checked at 10th post transplant day, 1 month post transplant, at the onset of PTE, and 2 years post transplant.

Data is expressed as mean ± SD or percentage as appropriate. Chi square test and student 't test were used to compare categorical variables and continous variables respectively between those who developed erythrocytosis after transplant (PTE group) and those who did not develop erythrocytosis. The level of significance was taken as ≤ 0.05

Results

There were 200 renal transplants performed during the study period of April to December 2008, of these 40 developed PTE (HCT ≥51%) indicating a prevalence of 20%. Table-1 summarizes the demographic, clinical and laboratory parameters of two groups. Although both groups had male preponderance, almost all patients in PTE group were males (P=0.004) .Their mean age was 29.63±8.78 years which was very similar to the other group. Patients with erythrocytosis had a relatively shorter duration of pre transplant dialysis (P=0.007). The groups were other wise very similar as regards, primary renal disease, type of antihypertensive medications and degree of HLA matching .Almost all patients in the two groups were on triple immunosuppression with equal proportion being on cyclosporine treatment. The mean time of onset of PTE was 9.5±2.5 months after transplantation. As expected peak values of haemoglobin and haematocrit were significantly different in patients with and without PTE. Average level of Hb and Hct at onset of PTE was 16.79±0.75 g/dl and 54.74±1.96% respectively (Figure-1, 2). Renal functions were significantly better at the onset of PTE in the same group, with mean serum creatinine being 1.06 ± 0.29 mg/dl compared to 1.37 ± 0.51 mg/dl in non PTE group around the same time. PTE group maintained excellent graft function till their last follow up. Table-2 shows laboratory data of patients with PTE. All patients with PTE were treated with enalapril (ACE inhibitors) and 28 out of 40 required phlebotomy in addition to ACE inhibitor. The mean HCT at the end of follow up in treated patients was 48.61±1.85% Table 3. None of the patients with erythrocytosis had hydronephrosis or transplant renal artery stenosis on doppler ultrasound study of transplanted kidney.

Table-1: Demographic Clinical and Laboratory Parameters. Comparison between PTE and non-PTE patients.

Parameter	PTE n=40	Non-PTE n=160	p-value
Sex Ratio Male / Female	38/2	118/42	0.004
Age (years)	29.63±8.76	28.69 ±9.81	
Smoking	14(35%)	45(28%)	
Original Disease			
Glomerulonephritis	7 (17.5%)	25 (15.6%)	
Hypertension	15(37.5%)	39(24.4%)	
Alports	1(2.5%)		
Stone disease	1(2.5%)	32(20%)	
Unknown Cause	19(47.5%)	68(42.5%)	
Beta Blocker	15 (37.5%)	38(23.8%)	
Calcium Channel Blocker	34 (85.0%)	140 (87.5)	
Immunosuppression			
Cyclosprine / Tacrolimus	33 / 7	146 / 14	
Steroids	40	160	
Azathioprine / MMF	32/8	137/23	
Pre-transplant transfusions			
Patients: n:	37	151	
Mean blood units: n:	3.68±2.53	3.71±3.05	
Duration on dialysis (months)	9.48±7.88	14.56±7.85	0.007
Peak Haemoglobin (g/dl)	16.79±0.75	11.88±1.62	0.001
Haematocrit (%)	54.78 ± 1.96	37.85 ± 5.03	0.001
Creatinine(mg/dl)	1.06 ± 0.29	1.37 ± 0.51	0.001
Acute rejection episodes	13(32.5%)	20 (12.5%)	0.002

Table-2: Laboratory data of patients with post-transplant erythrocytosis.

	Hb (g/dl)	HCT %	S. Cr (mg/dl)
10th post Transplant day	9.15 ± 1.15	27.13 ± 3.84	1.80 ± 1.09
1 month post Transplant	11.60 ± 1.51	36.14 ± 5.46	1.20 ± 0.34
At onset of PTE	16.79 ± 0.75	54.78 ± 1.96	1.06 ± 0.29
End of Follow-up	15.17 ± 1.72	48.61 ± 1.85	1.00 ± 0.35

Hb= Haemoglobin, HCT= Haematocrit, S. Cr.= Serum Creatinine.

Table-3: Treatment of PTE patients.

Angiotensin converting enzyme inhibitors (ACE - I)	12 pateints
ACE- I + phlebotomy	28 patients

	Before Treatment	After treatment
Haemoglobin g/dl	16.79 ±0.75	15.17±1.72
Haematocrit %	54.78±1.96	48.61±1.85

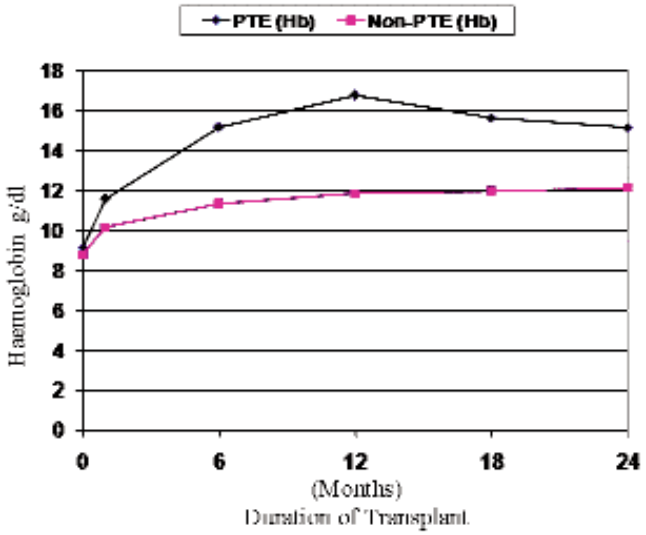

Figure: Evaluation of Haemoglobin levels in relation to duration of transplant.

Discussion

The prevalence of post transplant erythrocytosis (PTE) in our study is 20% which is close to the higher prevalence reported from other centres.[1] Patients with erythrocytosis were mostly males (95%) which is in agreement with other studies showing that PTE is more common in males. The meantime of onset of PTE in our study was slightly earlier compared to other studies.[1]

Erythrocytosis generally develops in those renal transplant recipients who have good renal function and without evidence of acute and chronic rejection.[1] In our study PTE patients had excellent graft functions, with mean serum creatinine of 1.06±0.29mg/dl at the onset of PTE. At the end of follow up the serum creatinine was 1.00±0.35 mg/dl. Patients with post transplant erythrocytosis in our study had a higher value of acute rejection episodes, which is rather unexpected and contrary to most previous studies showing that PTE occurs in those who had rejection free course before developing erythrocytosis. In 7 out of 13 patients who had acute rejection in PTE group, episode of acute rejection occurred well after development of erythrocytosis suggesting that acute rejection episode was non contributing to erythrocytosis. In remaining 6 patients acute rejection preceded PTE. In all these later patients rejection occurred in early transplant period with good reversal. Their renal functions were normal at the onset of PTE with mean serum creatinine being 1.15±0.40 mg/dl .At the end of follow up the serum creatinine in this sub group was 1.20±0.34 mg/dl .Therefore in our study acute rejection episodes were coincidental in PTE group.

The results on the influence of immunosuppressive therapy on the frequency of PTE are conflicting. Some studies have found that PTE occurs more frequently in cyclosporine-treated patients compared with azathioprine and prednisolone.[5,6] Almost all patients in the two groups in our study were on triple immunosuppression with equal proportion being on cyclosporine treatment. There was no relation between cyclosporine and erythrocytosis in our study. The other suggested causes of PTE include native kidney disease, the duration on dialysis, smoking habits and transplant renal artery stenosis.[11] 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. We did not encounter any case with transplant renal artery stenosis.

A number of therapies are available for the management of PTE. When haematocrit values exceed 55% therapeutic phelebotomy is required to maintain haematocrit around 50% to minimise the risk of thromboembolic events.[7] However a more conservative medical treatment suffices at a lower haematocrit level. RAS (renin angiotensin system) inactivation by ACEI and angiotensin receptor blocker (ARB).[9,10,12] Blockade of renal A2 adenosine receptor by theophylline has been shown to reduce erythropoietin secretion.[13] In our study PTE was diagnosed early and in majority treated with phlebotomies and angiotensin converting enzyme inhibitors, 12 patients who were treated with ACE inhibitors without phlebotomy had relatively lower level of peak haematocrit (52%) when ACE inhibitors were prescribed. None of PTE patients had thrombotic complications and all the patients maintained good renal functions during the follow up.

We did not measure erythropoietin (EPO) level in this study because of non availability of the test in our setup. Erythropoietin plays a pivotal role in erythropoiesis. Rejection episodes and transplant renal artery stenosis induces ischaemia and may thus increase erythropoietin production.[14,15] Erythropoietin levels were not measured in this study, but other studies have shown that EPO levels can be higher or within normal limits.

Conclusion

PTE in our transplant recipients has the same prevalence as reported from other parts of the world. Our study confirms its frequent association with good graft function and male gender. Thrombotic complications were not encountered in our study and response to ACE inhibitor was good.

References

1. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. Kidney Int 2003; 63: 1187-94.
2. Einollahi B, Lessan-Pezeshki M, Nafar M, Pour-Reza-Gholi F, Firouzan A, Farhangi F, et al. Erythrocytosis after renal transplantation: review of 101 cases. Transplant Proc 2005; 37: 3101-2.

3. Prakash J, Singh S, Behur SK, Ghosh B, Sharatchandra LK, Dwivedi US. Early posttransplant erythrocytosis in renal allograft recipients. J Assoc Physicians India 2010; 58: 574-6.
4. Razeghi E, Kaboli A, Pezeshki ML, Meysamie AP, Khatami MR, Khashayar P. Risk factors of erythrocytosis post renal transplantation. Saudi J Kidney Dis Transpl 2008; 19: 559-63.
5. Gruber SA, Simon RL, Najarian JS et al. Post transplant erythrocytosis and the risk of thromboembolic complications; correlation from a prospective randomized study of cycloserine versus azathioprine antithymocyte globulin. Clinc Transpl 2004; 2: 433-9.
6. Ghahramani NL, Malek-Hosseini SA, Rais-Jalali GA, Behzadi S, Nezakatgoo N, Salahi H, et al. Factors relating to posttransplant erythrocytosis in renal allograft recipients. Transplant Proc 1998; 30: 828-9.
7. Kazory A. Post-transplant erythrocytosis and thromboembolic events: an error. Nephrol Dial Transplant 2004; 19: 260.
8. Barenbrock M, Spieker C, Rahn KH, Zidek W. Therapeutic efficiency of phlebotomy in posttransplant hypertension associated with erythrocytosis. Clin Nephrol 1993; 40: 241-3.
9. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. Am J Transplant 2007; 7: 2350-60.
10. Mazzali M, Filho GA. Use of aminophylline and enalapril in posttransplant polycythemia. Transplantation 1998; 65: 1461-4.
11. Abdelrahman M, Rafi A, Ghacha R, Qayyum T, Karkar A. Post-transplant erythrocytosis: a review of 47 renal transplant recipients. Saudi J Kidney Dis Transpl 2004; 15: 433-9.
12. Kedzierska K, Kabat-Koperska J, Safranow K, Domanski M, Golembiewska E, Bober J, et al. Influence of angiotensin I-converting enzyme polymorphism on development of post-transplant erythrocytosis in renal graft recipients. Clin Transplant 2008; 22: 156-61.
13. Bakris GL, Sauter ER, Hussey JL, Fisher JW, Gaber AO, Winsett R. Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. N Engl J Med 1990; 323: 86-90.
14. Mossuz P, Girodon F, Donnard M, Latger-Cannard V, Dobo I, Boiret N, et al. Diagnostic value of serum erythropoietin level in patients with absolute erythrocytosis. Haematologica 2004; 89: 1194-8.
15. Qunibi WY, Barri Y, Devol E, al-Furayh O, Sheth K, Taher S. Factors predictive of post-transplant erythrocytosis. Kidney Int 1991; 40: 1153-9.