Introduction

Post-transplant polycythemia or post-transplant erythrocytosis (PTE) is defined as increased level of haemoglobin (Hb) (>17 gm/dl) persisting for >6 months. PTE occurs in 10-15% of renal transplant recipients and is usually common after 6-12 months of the transplant. It only reflects the rise in red blood cells (RBC) mass, while leukocytes and platelet counts remain normal. Spontaneous remission is observed in 25% patients. There are multiple risk factors for PTE which include male gender, smoking, presence of native kidneys, diabetes, renal artery stenosis of the transplanted kidney and the absence of rejection episode after transplantation. Aetiology of native kidney diseases, like polycystic kidney disease and glomerulonephritis, also increase PTE risk. It is also prevalent in patients who receive simultaneous kidney and pancreas transplants.

The pathogenesis of PTE is multifactorial. One of the major causes is sufficient production of erythropoietin by normal functioning graft and the absence of inhibitors of bone marrow erythrocytosis after correcting the uremia. The hormonal systems play an important role in pathogenesis which include erythropoietin, renin angiotensin system (RAS) and androgens. Erythropoietin is produced by peritubular fibroblasts. The presence of native kidneys is another important factor for PTE development. Native kidneys lead to increased secretion of erythropoietin even in the presence of erythrocytosis, and this phenomenon is termed tertiary hyper-erythropoitenemia. There is a relationship between secretion of erythropoietin and PTE development. It is also postulated that in PTE patients, there is increased sensitivity of erythroid progenitors to erythropoietin in vitro compared to those patients who do not have PTE.

When RAS is activated, it stimulates erythropoiesis and leads to PTE development. It is suggested that angiotensin-1 receptors (AT1) are also involved in the pathogenesis of PTE. RAS increases the production of erythropoietin in the native or the transplanted kidney, and activates RBC precursor in bone marrow. It also stimulates the production of erythropoietin by activation of hypoxia inducible factor (HIF). Angiotensin II increases the production of erythropoietin stimulated proliferation of erythroid progenitors. Androgens can also increase erythropoiesis as a result of their direct effect on erythropoietin receptor and RAS activation. For the same reason, PTE is more frequently seen in male patients compared to females.

Non-erythropoietin-mediated mechanisms also play an important role in PTE development. They include insulin like growth factor-1 (IGF-1) and serum soluble stem cell factor (sSCF). Post-transplant erythrocytosis is usually absent in patients with preserved graft in cadaveric transplantation.

PTE is diagnosed by the presence of Hb >17gm/dl and/or haematocrit >51% that persists for >6 months after renal transplantation and while other causes of erythrocytosis, like malignancy, chronic obstructive pulmonary disease

Abstract

Objective: To calculate the incidence of post-transplant erythrocytosis, and to assess the response to treatment.

Method: The prospective study was conducted from April 2016 to April 2018 at the Department of Nephrology, Bahria International Hospital, Lahore, Pakistan, and comprised patients undergoing renal transplantation who were evaluated and followed up for 12 months. Patients having haemoglobin levels ≥17gm/dl were labelled as having polycythemia. Data was analysed using SPSS 21.

Results: Of the 94 total patients, 69(73.4%) were enrolled. During follow-up, 2(2.9%) of them died, and, thus, the final sample stood at 67(71.3%); 57 (85%) males and 10(15%) females. The mean age of the sample was 32.6±8.8 years. Overall, 19(28.4%) patients developed polycythemia and they were either given angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Of these 19 patients, 11(57.8 %) responded to the treatment, while 8(42.1%) required phlebotomy. Further, 3(15.7%) patients required one phlebotomy, while 5(26.3%) who had glomerular filtration rate >30% had to have repeated phlebotomy.

Conclusion: The incidence of post-transplant erythrocytosis was significantly high at 28.4%.

Keywords: Post-transplant polycythemia, Erythrocytosis, Renal transplant. (JPMA 71: 889; 2021)

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(COPD) and congestive cardiac failure (CCF), are excluded. About 60% PTE patients usually suffer from malaise, headache, dizziness and plethora, whereas 10-30% may experience thromboembolic events presenting as thrombophlebitis, deep venous thrombosis (DVT) and stroke. It has been found that serum erythropoietin levels are poorly correlated with PTE.

Mainstay of PTE treatment is inhibition of RAS. This is achieved by administering angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs), but ACE-Is are more effective than ARBs in lowering its levels. Theophylline is also effective in PTE treatment, but it has a narrow therapeutic index and can cause serious side effects even at low dose. It also requires regular monitoring of drug levels. Moreover, it has no effect in PTE patients with normal erythropoietin levels. Ketanserin is a 5 hydroxytryptamine receptor (5HT2) antagonist and decreases erythropoietin levels, but it is not widely used. Different immunosuppressants have been associated with different effects on erythropoiesis due to their anti-proliferative effects. Patients on sirolimus have less incidence of PTE compared to those who are taking mycofenolate mofetil. But even then immunosuppressive regimen is usually not modified for the treatment of PTE.

Only patients who do not respond to ACE-Is or ARBs are managed with serial phlebotomies. It is effective in decreasing haematocrit levels, but can also lead to iron-deficiency anaemia. Phlebotomy can also be used in combination with ACE-Is or ARBs.

The current study was planned to calculate PTE incidence, and to assess the response to treatment.

Patients and Methods

The prospective study was conducted from April 2016 to April 2018 at the Department of Nephrology, Bahria International Hospital, Lahore, Pakistan. After approval from the institutional ethics review board, the sample was raised from among patients of both genders undergoing live related renal transplantation. Those with pre-transplant history of phlebotomy and/or use of ACE-Is or ARBs, had COPD, were smokers, had history of native kidney nephrectomy or a previous graft loss were excluded.

After taking informed consent from the subjects, they were followed up for 12 months from the time of transplantation. Patients having Hb ≥17 gm/dl were labelled as having PTE. After doing Doppler ultrasounds to exclude transplanted renal artery stenosis, all PTE patients were given ACE-Is or ARBs as the initial treatment, whereas phlebotomy was done only when there was inadequate response for 3 months. All the patients were monitored for Hb levels and glomerular filtration rate (GFR) on a monthly basis. ACE-Is and ARBs were withdrawn if there was fall in GFR of >30%.

Data was analysed using SPSS 21. Comparison between PTE and non-PTE patients at first follow-up post-transplant for serum creatinine, Hb, GFR and blood pressure (BP) was done using independent sample t test, and comparison of tacrolimus and cyclosporine was done using chi-square test. P<0.05 was considered significant.

Results

Of the 94 total patients, 69(73.4%) were enrolled. During follow-up, 2(2.9%) of them died, and, thus, the final sample stood at 67(71.3%); 57 (85%) males and 10(15%) females. The mean age of the sample was 32.6±8.8 years. Of the total, 60(89.6%) patients were on tacrolimus and 7(10.4%) were on cyclosporine. Overall, 19(28.4%) patients developed PTE; 18(94.7%) males and 1(5.3%) female. Of the PTE patients, 11(57.8%) responded to the treatment, while 8(42.1%) required phlebotomy; 3(15.7%) requiring one phlebotomy and 5(26.3%) with GFR >30% had repeated phlebotomy. Of the patients requiring multiple phlebotomy sessions, 4(7.1%) were males and 1(9.1%) was female. All of them were on triple-drug immunosuppression comprising prednisolone, mycofenolate and either tacrolimus or cyclosporine.

Chronic glomerulonephritis was the cause of end-stage renal disease (ESRD) in 50(74.6%) patients, while 10(14.9%) had diabetic nephropathy, 3(4.4%) had nephrolithiasis and 4(5.9%) had autosomal polycystic kidney disease (ADPKD). Baseline mean Hb concentration was 11.6±1.3 g/dl, creatinine 1.23±0.43 mg/dl and GFR 74.2±7.1 ml/min.

Across the 12-month follow-up, the PTE prevalence and incidence were monitored (Table 1).

Table 1: Prevalence and incidence of polycythemia in post-renal transplant patients.

<table>
<thead>
<tr>
<th>Time</th>
<th>Polycythemia status by month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence n (%)</td>
</tr>
<tr>
<td>Month 1</td>
<td>-</td>
</tr>
<tr>
<td>Month 2</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Month 3</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Month 4</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 5</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 6</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 7</td>
<td>9 (13.4)</td>
</tr>
<tr>
<td>Month 8</td>
<td>9 (13.4)</td>
</tr>
<tr>
<td>Month 9</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 10</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 11</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Month 12</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Total</td>
<td>72 (8.96)</td>
</tr>
</tbody>
</table>
The mean duration of PTE development was 5.6±2.5 months post-transplant. At the first follow-up, mean values of Hb, creatinine, GFR, systolic and diastolic BP were compared between PTE and non-PTE patients (Table 2). There was no statistically significant difference between the groups except for Hb (p<0.001).

Hb levels of those requiring multiple sessions of phlebotomy were monitored (Figure 1), and the same was the case with Hb (Figure 2) and GFR (Figure 3) levels of the entire sample.

**Table-2: Comparison of polycythemic and non-polycythemic patients.**

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
<th>Polycythemic patients</th>
<th>Non-polycythemic patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.23 ± 0.43</td>
<td>1.16 ± 0.29</td>
<td>1.26 ± 0.48</td>
<td>0.414</td>
</tr>
<tr>
<td>Haemoglobin (gm/dl)</td>
<td>11.6 ± 1.3</td>
<td>12.8 ± 1.1</td>
<td>11.1 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>74.2 ± 7.1</td>
<td>76.9 ± 8.1</td>
<td>73.1 ± 6.5</td>
<td>0.048</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>123.8±8.4</td>
<td>124.5±8.1</td>
<td>123.5±8.6</td>
<td>0.687</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.6±5.2</td>
<td>80.3±5.2</td>
<td>80.7±5.3</td>
<td>0.745</td>
</tr>
<tr>
<td>Drug used: Tacrolimus</td>
<td>60</td>
<td>18</td>
<td>42</td>
<td>0.354</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

†(Mean Values at 1st follow up visit after kidney transplant)

GFR: Glomerular filtration rate; BP: Blood pressure.

**Discussion**

In the current study, 28.4% patients developed PTE which is higher compared to previous studies done in Pakistan and worldwide. Reasons could be male predominance, presence of native kidneys, and absence of acute rejection episode, tacrolimus use and initial GFR of 74.3±7.1 ml/min in the current study. None of the patients underwent native nephrectomy. This may have led to a sustained release of erythropoietin by the native kidneys, contributing to PTE, as previously discussed in a literature. Initial mean GFR of 74.3±7.1 ml/min is well rationalised by the fact that in all the transplants, the recipient and the donor were close family members with good HLA matching and minimum ischaemic time. This relationship of PTE with stable and good renal functions has also been established. Although the difference between higher GFR in PTE patients and that of non-PTE patients was not significant, a bit higher GFR in the former group may indicate a relationship of PTE with graft function. Though a recent study has demonstrated association of PTE with tacrolimus use, in the present study, 18 out of 60 patients (30%) on tacrolimus and 1 out of 7 patients (14.2%) on cyclosporine developed PTE (p>0.05). The failure to establish an association of PTE with immunosuppression might be because of smaller number of patients on cyclosporine in the current study.

As 57 patients (85%) were males and 10 patients (15%) were females, the reason for male predominance as transplant recipient is linked to social setup of our male-dominated community, and males are more prone to polycythemia due to hormonal effect of androgens. It is also worth mentioning that the initial Hb level had a statistically significant correlation with PTE, as polycythemic patients had a higher initial Hb level compared to those who did not develop PTE later on.

To the best of our knowledge, this is second study in Pakistan which has also evaluated the response of ACE-Is and ARBs in the treatment of post-transplant PTE. Fourteen patients (73.6%) responded to treatment with ACE-Is or ARBs + single phlebotomy, whereas 5 patients (26.4%) did not respond.
not respond to treatment and needed multiple phlebotomies. The same 5 patients who required multiple phlebotomies also required drug withdrawal due to fall in GFR >30% due to ACE-Is or ARBs, probably because of the relatively prolonged and higher dose of the drugs.

Inhibition of RAS system by ACE-Is / ARBs is the mainstay treatment for post-transplant PTE and the rate of response to ACE-Is / ARBs is in accordance with studies that showed around 80% response and while PTE may have variable numbers of thromboembolic complications, none of our patient developed such complications, which, again, has been reported in literature.

The current study has certain limitations as it was conducted at a single centre and the sample size was relatively small. Because of the poor correlation of serum erythropoietin level with PTE, higher cost and limited availability in the country, it was not measured in the current study.

Conclusion
PTE incidence over 12 months was significantly high at 28.4%. ACE-Is / ARBs were the mainstay of PTE treatment and majority of the patients responded well to it. A few patients also required additional phlebotomy sessions.

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Conflict of Interest: None.
Source of Funding: None.

References