ORIGINAL ARTICLE

MEDICAL COMPLICATIONS OF RENAL TRANSPLANT – 2 YEARS' EXPERIENCE AT ARMED FORCES INSTITUTE OF UROLOGY

Zahid Farooq Baig, Umair Ahmed Siddiqui, Arshad Mahmood, Haroon Sabir, Tariq Bashir Tareen

Armed Forces Institute of Urology, Rawalpindi-Pakistan

Background: Renal transplant is the renal replacement therapy of choice for all patients of chronic kidney disease. The aim of this study was to analyse the trends of medical complications in renal transplant recipients at our centre. **Methods**: it is a prospective cross sectional descriptive study. All the patients undergoing renal transplant at Armed Forces Institute of Urology from September 2013 to September 2015 were included in the study. The patients were followed prospectively till March 2016 and a complete data about their complications and lab investigations was maintained. **Results**: This study included a total of 63 patients with a mean duration of follow-up of 14.05 months (SD±4.45). Infective complications as a group are the commonest complication occurring in over 50% of cases followed by haematological complications (17.5%), new onset diabetes after transplant (15.9%) and transplant dysfunction (14.3%) Cardiovascular complications were seen in only 4.8% cases but with high mortality. Gingival hypertrophy was seen in 4.8% cases. **Conclusion**: Medical complications are common after renal transplant especially in the early post-operative period. The only way forward is early recognition and aggressive treatment, as delays can cost losses in the form of kidney function, life and higher health care cost.

Keywords: Renal transplant; Medical complications; AFIU; Pakistan

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INTRODUCTION

After the first successful renal transplant (RT) by Dr. Joseph E. Murray on 23rd December 1954, we in Pakistan had to wait for another 25 years for the first RT to happen. This was done on 18th March 1979 in Combined Military Hospital Rawalpindi. This was the beginning from where it has continued in all major cities of Pakistan. Today with the utmost efforts of Dr Adibul Hassan Rizvi and his team, Sindh Institute of Urology and Transplantation (SIUT) is running the largest free kidney transplant program in Asia.[1]

Renal Transplant is the replacement therapy of choice for patients of end stage renal disease (ESRD).[2] In comparison to long term haemodialysis (HD), a successful RT improves the quality of life and increases survival for most patients with ESRD.[3–5] RT is also more cost-effective, thereby decreasing health care costs.[6] It is associated with complications that impair the quality of life of transplant recipient and also add to health care cost.

The aim of this study was to analyse the trends of medical complications in RT recipients at our centre.

MATERIAL AND METHODS

This is a cross sectional descriptive study, carried out prospectively in patients with chronic kidney disease (CKD), who underwent RT at Armed Forces Institute of Urology (AFIU) Rawalpindi, from September 2013 to September 2015.

The pre-transplant workup was carried out in department of Nephrology AFIU, according to standardized guidelines. All cases underwent final approval from Human Organ Transplant Authority (HOTA) prior to transplant.

As per protocol immunosuppression was started twelve hours before surgery. The first dose of calcineurin inhibitor (CNI) is given twelve hours before and the second dose on the morning of RT along with Mycophenolate. Injection Methyl-Prednisolone was administered 1 gram per operative and 500 mg daily for 2 days and then patient shifted to oral prednisolone. Induction therapy with Basiliximab or anti thymocyte globulin (ATG) was only given to young patients less than 20 years of age and high-risk patients, i.e., those with any historic cross match positive. In CNIs ciclosporin was the main drug used and tacrolimus only administered to females or young boys. Trimethoprim/Sulfamethoxazole and Cytomegalovirus (CMV) prophylaxis was administered to all the patients.

Post-transplant patient was observed in a designated post-operative intensive care unit. A complete record of vital signs, intake output, lab investigations and treatment was maintained. The CNI drug levels were carried out at day three and day six. Once the patient is considered fit he was discharged and followed up in outpatient department. Initially he was followed up twice weekly for first month post-transplant, then once weekly for another month, then

fortnightly for one month and after that monthly, unless there was some problem.

A complete record of visits was maintained including a data of investigations and complications. Chronic glomerulonephritis is defined by the presence of bilaterally small kidneys at the time of presentation, with deranged renal functions and presence of hypertension. New onset diabetes after transplant (NODAT) was defined as per international consensus guidelines 2003.[7] Acute rejection was defined as acute deterioration of renal functions with rise of creatinine of more than 25% from baseline level. This was repeated once and if confirmed renal transplant biopsy was performed. CMV disease was defined by presence of positive CMV-DNA-PCR accompanied by clinical signs and symptoms. Post kidney transplant erythrocytosis is defined as a persistently elevated haematocrit to a level greater than 51% after renal transplantation.

Data was collected on computerized forms using Microsoft Access 2013 Database and was analysed using SPSS version 22. Descriptive stats were summarized as percentages, ratios and means with standard deviation for different parameters observed in transplant patients. Statistical significance of differences observed between two groups (patients who survived and those who did not survive after transplant) was done using students t-test for continuous data and chi square for categorical data, *p*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 63 patients underwent RT during study period. The mean duration of follow-up was 14.05 months (SD±4.45). There was no case of pre-emptive renal transplant and the mean duration of HD before RT is 137.24 days (~4 ½ months).

Our transplant population is young, the mean age of recipients is 33.16 years (SD±8.99), with donors being a year younger with mean age of 32.13 years (SD±9.17). In gender males are the main recipients with male to female ratio of 5.99 (85.7/14.3), while females are the predominant donors with ratio of 2.1 (68.3/31.7). The donor relation to recipient depicted fathers as donors in 1.6% cases, mothers (7.9%), brothers (22.2%), sisters (41.3%), wives (20.6%) and son (6.3%). There were no donations from daughters and husbands in our study.

The blood group of recipients in order of frequency included A (42.9%), B (27%), O (23.8%) and AB (6.4%) while in donors it was A (39.7%), O (31.8%), B (25.4%) and AB (3.2%).

Antigen match in HLA typing included zero match in 9.5% cases, one antigen match (7.9%), two antigen matches (6.3%), three antigen matches (47.6%), four antigen matches (14.3%), Five antigen match (7.9%) and six antigen matches (6.3%).

As far as pre-transplant CMV status is concerned 76.1% were recipient and donor positive, 12.7% were recipient and donor negative while recipient positive donor negative 7.9% and recipient negative donor positive 3.2% cases. Around thirteen percent (12.7%) of the recipients were Hepatitis C positive with no case of Hepatitis B.

Glomerulonephritis is the commonest cause of CKD in our patients seen in 50.7% cases, Diabetes mellitus (11.1%), and obstructive nephropathy 4.8% cases. In 33.3% cases, exact cause of CKD could not be determined (Table-1).

Induction therapy was given in only selected cases as per protocol and 85.7% cases did not receive any induction while 12.7% received Basiliximab and 1.6% ATG. For maintenance immune-suppression all patients received Mycophenolate mofetil and steroids. In CNIs, Ciclosporin was given to majority of patients, i.e., 77.8% and Tacrolimus to only 22.2% cases.

The transplant patient encounters a variety of complications. The medical complications which we encountered in our patient population are shown in table-2.

Five of our patients (7.9%) died during follow-up. One patient had acute myocardial infarction on second post-op day and another had acute pulmonary embolism on fifth post-op day. Three of our patients died of severe sepsis leading to septic shock and multi-organ failure. Interestingly none of these three patients had received induction therapy. Table-3 shows a comparison of variables between patients who were alive at the end of follow-up and those who died.

At the end of follow-up period the mean creatinine level was 121.38 (SD±23.[6]

Table-1: Primary renal disease in renal transplant recipients

Primary diagnosis	AFIU data	UK data*	India [10]
Aetiology unknown	33.3	12.3	-
Diabetes mellitus	11.1	13.3	8.16
Glomerulonephritis	50.8	22.3	60.2
Polycystic kidneys	-	13.7	2.04
Pyelonephritis	-	9.9	-
Renovascular disease	-	8.1	-
Interstitial nephritis	-	-	15.31
Others	4.8	16	14.29

*As per UK Renal Registry 17th annual report – 2014.

Table-2: Medical complications in renal transplant recipients

Medical complications	Frequency in our study	Frequency as per international data with reference
New onset diabetes after transplant (NODAT)	15.9% (n=10)	4–25% [7]
Transplant dysfunction	14.3% (n=9)	
a) Acute transplant rejection	12.7% (n=8)	10% [21]
b) Chronic allograft nephropathy	1.6% (n=1)	
Infective complications	52.4% (n=33)	
a) Sepsis	14.3% (n=9)	10.4% [13]
b) CMV disease	14.3% (n=9)	5% [21]
c) Hep C infection	12.7% (n=8)	5–60% [18]
d) Pulmonary tuberculosis	3.2% (n=2)	3.1–15% [23]
e) Fungal infections	6.3% (n=4)	1.4–14% [25]
Haematological complications	17.5% (n=11)	
a) Anaemia requiring intervention*	9.5% (n=6)	17.8% [27]
b) Post-transplant erythrocytosis	7.9% (n=5)	10–15% [29]
Cardio-vascular complications	4.8% (n=3)	3.5–5% [32]
a) Acute myocardial infarction	3.2% (n=2)	
b) Pulmonary embolism	1.6% (n=1)	
Gingival hypertrophy	4.8% (n=3)	27%

*Intervention means administration of IV Iron, Erythropoietin or red cell concentrate (RCC).

Table-3: Comparison of patients according to mortality status post renal transplant

Variables	All patients (n=63)	Patients who died (n=5)	Alive patient (n=58)	*p*-value
Gender male recipient	85.7%	100%	84.48%	0.341
Age recipient	33.16±8.99	42.2±12.56	32.38±8.31	**0.018**
Age donor	32.13±9.17	29.4±9.31	32.36±9.21	0.493
DM as the cause of CKD	11.1%	40%	8.6%	**0.032**
Antigen mismatch	2.98	2	3.06	0.132
Induction therapy for Immuno-suppression	14.3%	None	15.5%	0.636
Pre-transplant haemodialysis days	137.24	146	136.48	0.878

DM – Diabetes mellitus, CKD – Chronic kidney disease

DISCUSSION

The age among donors and recipients has slowly shifted towards older age groups in developed countries in the last decade, with average age trending up to over 50 years.[8] Our transplant population is young and this is similar to other countries in the region with average age between 30 and 35 years.[9–12]

Gender disparity is present even in countries like United States and United Kingdom, with women getting a lower chance of receiving HD and RT than men, but they constitute the majority of living kidney donors.[13] In our study male to female ratio in recipients is almost 6 which is similar to other studies in Pakistan[9], This is in between UK data in which it is 1.6 and India where it is 7.99.[12] Economic factors such as greater income of men is the likely cause which may encourage males to be predominant recipients and females to be donors. In donor relations husbands are absent from our donor list probably for the same reason. The absence of daughters as donors is likely due to future fear of marriage problems. Sindh Institute of Urology and Transplantation as a policy do not accept donation from unmarried females.

In live donation antigen mismatch lack any impact on outcome of RT.[14,15] Majority of cases in our population were one haplotype or 3 antigen matches. Our transplant data is consistent with this.

The incidence of NODAT ranges from 4 to 25% in the international literature.[7] One of the most accurate incidence of NODAT under CNI therapy is provided by the prospective study of Vincenti *et al*[16], reporting an incidence of NODAT reaching 20.5% within the first 6 months post renal transplantation. In our transplant population, it is a bit lower 15.9%. A younger age group may be a possibility of this difference as older age is a strong independent risk factor of NODAT. There is a 90% increase of relative risk in renal transplant patients aged 45–59 and a 160% increase in patients more than 60 years (versus 18–44 years as a reference).[17] The other risk factors include positive hepatitis C virus (HCV) serology and a positive family history of type 2 diabetes.[18,19]

Acute rejection episodes are a major determinant of renal allograft survival, and the improvement of the transplantation results in the last two decades is largely due to a progressive decrease in the incidence of acute rejection.[20] The incidence of acute rejection is decreasing over time and is less than 10% after 2000.[21] Similar incidence was reported in United States Renal Data System in 2009. The incidence in our transplant population is a bit higher to 12.7%. Lack of induction therapy in majority of the patients can be the possible cause. All the patients underwent renal transplant biopsy and had cellular rejection which was completely reversed with treatment.

Chronic allograft nephropathy renamed as "interstitial fibrosis and tubular atrophy (IFTA)" is the major cause of failure of RT other than patient death[22], accounting for 25–30% cases awaiting renal transplantation. In our study one patient (1.6%) who was lost to follow up and developed this at twentieth month post renal transplant. This incidence is low due to short follow-up period in our study.

Infections are a major cause of morbidity and mortality in RT recipients. In a retrospective analysis carried out by Schachtner *et al* in 1013 patients, 10.4% patients studied were diagnosed with sepsis, among which 29.5% developed severe sepsis or septic shock, and 26.7% died from sepsis.[23] In our study population frequency of sepsis is higher and it developed in 14.3% cases with a mortality of 33.3% cases in these cases.

HCV infection is increasingly recognized as a major health care problem in Pakistan with an estimated frequency in our population ranging from 0.4% to 33.7% in different areas.[24] The situation is worse in HD patient with a frequency range of 14% to 38% and even up to 68% in some studies.[25–27] In developed countries, the prevalence of anti-HCV seropositivity among patients on maintenance HD ranges between 5% and 60%.[28] The data from USA collected from the Centres for Disease Control and Prevention shows the prevalence of positive serologic status for anti-HCV antibody of 8–10% which has apparently not changed significantly over the last years but is highly variable from unit to unit within the same country, with recent reports from some dialysis units in the USA reporting prevalence above 20%.[29] In our study group HCV infection was in 12.7% which is in the lower limit of frequency in HD patients in our country as well as developed countries.

Cytomegalovirus is one of the most frequently encountered opportunistic viral pathogens in renal transplantation with an incidence of over 20% before preventive strategies were started and now the incidence has reduced to 5% with modern approaches.[30,31] We in our centre used prophylactic approach but CMV disease in our study was high with frequency of 14.3%. In order to reduce the cost of treatment we used acyclovir and valacyclovir for prophylaxis. Presently valgancyclovir is the therapy of choice for CMV prophylaxis and disease among transplant recipients with excellent results. The problem with valgancyclovir is a very high cost in Pakistan.

Tuberculosis (TB) is one of the leading infections following RT. Reactivation is the most common mode of infection.[32] The reported prevalence of post-transplant TB is 3.1–15% in Asia, 1.5–8.5% in South Africa, 1.5–3.5% in the Middle East, 1.7–5% in Europe and 1.5% in the United States.[33] We had pulmonary TB in only 3.2% cases in our study; they were treated with anti-TB drugs and responded. Another study at SIUT reported an incidence of 11% in Pakistani population.[34]

Renal transplant is associated with the lowest incidence of invasive fungal infection of all solid organ transplantations with a total incidence of 1.4–14% invasive fungal infections. Out of these zero to 10% are due to aspergillosis and 90–95% are caused by candidiasis.[35] Invasive aspergillosis if present in transplant recipients is associated with a significant mortality rate.[36] In our study, invasive fungal infection developed in 6.3% cases. Invasive pulmonary aspergillosis occurred in one patient with pulmonary TB and was treated with decrease in immunosuppression and liposomal amphotericin B to which he responded. Invasive candidiasis was seen in three cases that were treated with fluconazole to which they responded.

Anaemia is common after RT. The Transplant European Survey on Anaemia Management (TRESAM) documented the prevalence and management of anaemia in kidney transplant recipients.[37] At enrolment, 38.6% of patients were found to be anaemic. Of the 8.5% of patients who were considered severely anaemic, only 17.8% were treated with epoetin. In another study anaemia was present in 39.7% of the patients and prevalence of iron deficiencies, as indicated by a percentage of hypochromic red blood cells was 20.1%.[38] In our study population anaemia requiring intervention was seen in 9.5% cases. All of these cases received IV Iron and 2 requiring RCC transfusion.

Post RT erythrocytosis occurs in 10–15% of graft recipients and usually develops 8 to 24 months after engraftment.[39] Another study from Pakistan has reported an incidence of 20% after a mean interval of 9.5±2.5 months.[40] In our study, it developed in 7.9% cases. This was controlled with theophylline and losartan in all cases except one who initially needed repeated venesection but was later controlled with these drugs. There were no thrombo-embolic events in any of these cases.

Renal transplant recipients have a markedly increased risk of premature cardiovascular disease[41], the annual risk of a fatal or non-fatal cardiovascular event of 3.5–5% in renal transplant recipients is 50-fold higher than the general population.[42] Prevalence of pulmonary embolism in patients with RT is lower than those with chronic HD but higher than the general population. Cardiovascular complications occurred in 4.8% cases in our study, 2 patients developed acute myocardial infarction which was fatal in one case, despite the fact that none had clinically evident ischemic heart disease before

transplantation. One patient developed pulmonary embolism costing him with life.

Gingival hypertrophy (GH) is a rare condition and no population based or epidemiologic studies exist. The incidence rates are reported from case series studies. The prevalence of GH in transplant recipients on cyclosporine is estimated at 27% cases. In our study majority of patients were on ciclosporin for immunosuppression and GH was seen in only 4.8% cases in our patients and these patients responded to treatment with metronidazole and oral hygiene measures. The reason may be lower dose of ciclosporin as the incidence of GH is correlated with the dosage and serum level of the drug.[43]

The survival of RT recipients is significantly lower than age-matched controls in the general population but much superior to patients on HD. Cardiovascular disease is a major cause of graft loss and the leading cause of death in RT recipients followed by infections in developed countries[44,45] but in 1970s the situation was opposite[46]. In developing countries sepsis/infection is still the leading causing death followed by coronary artery disease.[12] There was a mortality rate of 7.9% in our study during follow-up period. As infectious diseases are high in our country similar to other developing countries, it was the leading cause of death in our study responsible for 60% deaths and cardiovascular disease in the remaining 40% cases.

Comparison of patients according to mortality status is given in table-3. The variable that had a significant negative influence on patient survival in our transplant population include recipient's age and diabetes as a cause of CKD. This is in accordance with the international data, which conclude that the survival of patients of RT has improved considerably over the past few decades, but older age and co-morbidity such diabetes mellitus still pose the risk of mortality.[16,46]

CONCLUSIONS

Renal transplant promises a longer and better quality of life for patients on renal replacement therapy but this is at the cost increased risk of some medical complications. The only way forward is early recognition and aggressive treatment of these which requires multi-disciplinary team approach with major inputs by nephrologist, urologist and intensivist, an excellent laboratory and radiology support and well-established hospital protocols and trained paramedics.

Conflict of interest: This study has no conflict of interest to be declared by any author.

AUTHORS' CONTRIBUTION

ZFB: Conceptualization of study design, literature review, data collection, write-up. UAS: Conceptualization of study design, proof reading. AM: Conceptualization of study design, proof reading. HS: Data collection, proof reading. TBT: Data collection and data analysis.

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Address for Correspondence:

Zahid Farooq Baig, Nephrologist, Combined Military Hospital, Multan-Pakistan
Cell: +92 323 510 0221
Email: zhd.frq@gmail.com