Original Article

Renal transplant in Nepal: medical complications in first three months

Shrestha S, Raut KB, Sigdel MR, Kafle MP, Shah DS

Department of Nephrology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Corresponding Author: Dr Shailendra Shrestha

Department of Nephrology, Tribhuvan University Teaching Hospital

Email: Shailendra_1975@hotmail.com

Abstract

Introduction: A successful renal transplant program was started in Nepal on August 8, 2008 in Tribhuvan University Teaching Hospital; and since then more than 200 live renal transplants have been done in our center.

Methods: A prospective analysis was done of 50 consecutive renal transplant recipients (performed from June 29, 2011 to May 16, 2012), with a minimum of 3 months of follow up. All recipients were on tacrolimus, mycophenolate mofetil, and steroids. The outcomes of the study were medical complications that occurred within the study period.

Results: The mean age of the recipients and donors were 36.0 ± 1.1 (range 15-59) and 48.3 ± 1.1 (range 22-65) years respectively. The fatal complications were one case each of hospital acquired pneumonia leading to sepsis, delayed graft function secondary to acute tubular necrosis, and community acquired pneumonia. The most common non fatal infection in first month post transplant was urinary tract infection, 24 episodes were identified in 20 recipients (40%). In 1 to 3 month post transplant also, urinary tract infection was the most common non fatal infection, 6 episodes occurred in 5 recipients (10%). 6 episodes of biopsy proven acute rejection occurred in 6 recipients (12%). Delayed graft function was observed in 2 patients (4%). New onset diabetes after transplant occurred in 6 patients (12%).

Conclusion: The most common medical complication in first three months post transplant was urinary tract infection, followed by acute rejection, new onset diabetes mellitus after transplant and delayed graft function.

Keywords: Recipient, renal, transplant,

Introduction

Chronic Kidney Disease (CKD) is recently grouped into Non Communicable Diseases (NCD) by Political declaration of the High-level Meeting of the United Nations General Assembly, and with its increasing incidence in developing nations, is rightly considered as a public health problem. [1, 2]

The estimated incidence of End Stage Renal Disease (ESRD) in Nepal is around 2900 new cases/year , based on the estimated ESRD incidence of about 100 cases/ million population/year in developing nations.[3] However, a recent population based study in India showed it to be around 232/ million population/ year[4], suggesting the incidence in Nepal may actually be higher. Unfortunately because of the lack of a renal registry in Nepal, the exact incidence and prevalence of ESRD in the country is not known.

Renal transplant is the treatment of choice for patients with ESRD. It not only restores life, but is also associated with higher survival rate, better quality of life and cost effective as compared to other modalities of Renal Replacement Therapy (RRT). However this service became available in Nepal only on August 8, 2008, when the live donor renal transplant program was started in Tribhuvan University Teaching Hospital. And since then more than 200 live renal transplants have been performed in our center. [5, 6]

Here we report the medical complications that occurred in first three months post transplantation, in 50 recipients.

Methods

A prospective observational study of 50 consecutive renal transplants recipients (performed from June 29, 2011 to May 16, 2012) was done and they were followed up for a minimum of 3 months post transplant. All the medical complications that occurred during the study period were recorded. The study was performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008.

A complete general, immunological and surgical work up of the donor recipient pair was performed according to the center's protocol. [7]

Methylprednisolone 500 mg, iv was given to all the recipients on the day of surgery. Anti Thymocyte Globulin (ATG) 1 mg /kg body wt, two doses, day 0 and 1, was preferred as an induction agent unless contraindicated either because of recent infections or financial constrains. All patients were initiated on Tacrolimus (TAC, 0.1 mg/kg in two divided doses, starting dose), Mycophenolate Mofetil (MMF, fixed dose of 2 gm/day in two divided doses, starting dose), and Wysolone (20 mg od for 1 month, then tapered at the rate of 2.5 mg/ week over next 5 weeks to 5 mg od, which was continued) as a triple immunosuppressive regime. TAC and MMF were started 48 hours prior to the elective surgery. Monitoring of tacrolimus trough level (Co) was done by Enzyme Immunoassay method to maintain the drug level between 10-12 ng/ml in first 2 weeks, 8-10 ng/ml between 2-6 weeks, 7-8 ng/ml between 6 weeks to 3 months, 5-7 ng/ml between 3 months to 1 year and 3-5 ng/ml thereafter. Monitoring of MMF level was not done; however, its dose was reduced to 500 mg tds after 1 month at the time of stable serum creatinine level. All patients also received oral clotrimazole lozenges for 1 month, oral valgancyclovir, 450 mg od for 3 months, and oral trimethoprim-sulfamethoxazole (80 mg-400 mg) for 1 year as infection prophylaxis.

Patients were discharged from the ward after about 5-7 days of the surgery when they achieve normal or near normal renal function. All recipients were followed up in transplant outpatient unit daily for first 5 days after discharge, on alternate days in second week, twice a day in third week, and once a day in fourth week. The frequency of follow up decreases with fortnightly visit in fifth week and once a month visit till the completion of third month. In all the visits, recipients underwent a complete physical examination and routine blood tests which include blood counts, renal function tests and urine routine examination. Besides, special investigations like Doppler Ultrasound scan of the graft kidney, renal biopsy were done as indicated.

The outcomes of the study were medical complications in first three months post transplant. Medical complications included Infections, Biopsy Proven Acute Rejections (BPAR), Acute Tubular Necrosis (ATN), Delayed Graft function (DGF), Recurrence of Primary Disease, New Onset Diabetes Mellitus After Transplant (NODAT), and hematological complications. BPAR was defined according to Banff 2007 update, DGF was defined as the need for haemodialysis in the first week post transplant. NODAT was defined according to American Diabetic Association (ADA) criteria and need to continue oral hypoglycemic drugs or insulin for more than 1 month. Urinary tract infection (UTI) was defined as a positive urine culture with signs and symptoms of upper or lower urinary tract infections. Findings from quantitative and qualitative tools were presented in tabular form, where mean ± SD, and percentage was calculated.

Results

The mean age of the recipients and donors were 36.0 ± 1.1 (range 15-59) and 48.3 ± 1.1 (range 22-65) years respectively. Among the recipients 43 (86%) were male, however, only 7 (14%) were female. In contrast to that only 17 (34%) donors were male and 33 (66%) were female.

Baseline characteristics of the recipients and donors are shown in table 1and table 2 respectively.

Table 1: Baseline characteristics of the recipients

Characteristics	Mean ± SD, N, %
Age (years)	36.0 ± 1.1, range 15 – 59
Sex	
M	43 (86)
F	7 (14)
Cause of ESRD	
CGN	22 (44)
HTN	13 (26)
IgA nephropathy	6 (12)
DM	5 (10)
FSGS	2 (4)
ADPKD	1 (2)
MPGN	1 (2)
Preemptive transplant	7 (14)
Mode of dialysis Hemodialysis CAPD **Duration of Dialysis (months)**	 46 (92) 4 (8) 4.5 ± 3.0
Hemoglobin	10.0 ± 2.0
Albumin	41.4 ± 2.0
Calcium	2.3 ± 1.3
Phosphorus	5.1 ± 1.4
CMV (IgG)	**all positive**
Duration of hospital stay (post transplant surgery)	6 days

ESRD, end stage renal disease, CGN, chronic glomerulonephritis, HTN, hypertension, IgA, immunoglobin A, DM, diabetes mellitus, FSGS, focal segmental glomerulosclerosis, ADPKD, adult polycystic kidney disease, MPGN, membranoproloferative glomerulonephritis, CAPD, continuous ambulatory peritoneal dialysis, CMV, cytomegalovirus, IgG, immunoglobulin G]

The Human Leucocyte Antigen (HLA) mismatch between the donors and recipients ranged from 0/0 mismatch to 6/6 mismatch.

Table 2: Baseline characteristics of the donors

Age (years)	**48.3 ± 1.1, range 22 – 65**
Sex	
M	17 (34)
F	33 (66)
Relation with the recipient	
Genetically related	35 (70)
Genetically unrelated	15 (30)
Wife	11
Husband	1.0
Father in law	1.0
Mother in law	1.0
Sister in law	1.0
CMV (IgG)	**All sero-positive found.**

Table 3: shows the immunological and surgical characteristics of the cohort.

Characteristics HLA mismatch	N (%), Mean ± SD
0	3 (6)
1	2 (4)
2	10 (20)
3	9 (18)
4	10 (20)
5	9 (18)
6	7 (14)
PRA	
<20 %	41 (82)
>20 %	9 (18)
Induction	
Yes	37 (74)
No	13 (26)
Side of donor nephrectomy	
Left	43 (86)
Right	7 (14)
First Warm Ischemia Time	87.9 ± 5.6 seconds
Cold Ischemia Time	32.1 ± 1.7 minutes
Second Warm Ischemia Time	36.0 ± 8.4 minutes

[HLA, human leukocyte antigen, PRA, panel reactive antibodies]

The most common non fatal infection in first month post transplant was urinary tract infection (UTI), 24 episodes were identified in 20 recipients (40%), and E. coli (13 episodes, 54%) was the most commonly isolated organism. Table 4 shows the infective episodes of first month post transplant.

Table 4: Infections within 1 month

Distribution of Infectious microorganisms	No.
Urinary Tract Infections	24
E. coli	13
Klebsiella pneumonia	4
Acinetobacter calcoaceticus baumanii complex	3
Pseudomonas aeruginosa	3
Citrobacter freundii	1
Hospital Accquired Pneumonia * (¶MRSA was isolated in one case and no growth in another)	2

[*One case of Hospital acquired pneumonia, where no organism was isolated was the fatal infection in post operative period, ¶ MRSA,methicillin resistant staphylococcus aureus]

In 1 to 3 month post transplant also, UTI was the most common non fatal infection, 6 episodes occurred in 5 recipients (10%), and E. coli accounted for 33% of total cases. Table 5 shows the infective episodes between 1-3 months post transplant.

Table 5: Infections between 1 to 3 months

Infections	No.
Urinary Tract Infections	6
E.coli	2
Klebsiella pneumonia	2
Acinetobacter calcoaceticus baumanii complex	1
Citrobacter freundii	1
Community Accquired Pneumonia, no organism isolated	1
Left epididymorchitis	1
Iliopsoas abscess (Tubercular)	1

[Fatal infection at the end of third month]

There were three fatal complications in first 3 months. First death occurred in a 51 years old multiparous female, who was on maintenance hemodialysis for about one year prior to transplant. She developed urinary leak in the post operative period followed by Antibody Mediated Rejection (AMR). Although AMR was treated with plasmapharesis + low dose intravenous immunoglobulins (IVIg), 0.1 gm/ kg body, she developed hospital acquired pneumonia after third session, need to be intubated and succumb to death on 12th day postoperatively.

Second death was in a 48 years old male with diagnosed ischemic heart disease as a comorbid condition prior to surgery. He had undergone bilateral nephrectomy for Adult Polycystic Kidney Disease (ADPKD), about 5 months before transplant. This patient had a fall in blood pressure during transplant surgery, which did not improve despite multiple ionotropic drugs. Patient was kept in mechanical ventilation post operatively, multiple sessions of haemodialysis was done for delayed graft function (secondary to acute tubular necrosis); however patient expired on 9th post operative day.

Third death was in a 58 years old diabetic ESRD patient, and he died of community acquired pneumonia at the end of 3 month, despite being treated with IV antibiotics and mechanical ventilation.

Death censored graft failure occurred in 2 patients; in first case the cause of graft failure was noncompliance of immunosuppressive drugs --- cortical necrosis of graft kidney (biopsy proved) graft nephrectomy at the end of second month. And in another case, patient started having pain and swelling at the graft site on 2nd post operative day; Ultrasonography revealed complex hematoma at peri-graft area, ultimately leading to reexploration and graft nephrectomy on the same day.

A total of 6 episodes of Biopsy Proven Acute Rejection (BPAR) occurred in 6 recipients (12%). Table 6 shows BPAR in first three months post transplant.

Table 6: Biopsy Proven Acute Rejections (BPAR) in first 3 months

Rejections	No.
Acute Cellular Rejection (ACR)	5
Borderline	2
Banff IIA	1
Banff IB	2
Antibody Mediated Rejection (AMR)	1

All episodes of ACR responded to IV Methyl Prednisolone (MP), 250 mg od for 3 days. In one case of ACR Banff IB, serum creatinine returned to baseline after 3 doses of MP, but proteinurea persisted, so IV ATG 1 mg/ kg body, 2 doses was given on 2 consecutive days. AMR was treated with 7 sessions of plasmapharesis + low dose intravenous immunoglobulins (IVIG), 0.1 gm/kg body.

Delayed Graft Function (DGF) occurred in 2 patients (4%) and the causes being Acute Tubular Necrosis (ATN) in one patient and Renal Artery Stenosis (RAS) of graft kidney in another one.

NODAT occurred in 6 patients (12%), and insulin was used for the control of blood sugar in all 6 patients. Temporary episodes of leucopenia occurred in 11 recipients (22%), however all episodes returned to normal after temporary discontinuation of tablets MMF, Valgancyclovir, and Cotrimoxazole for few days.

Discussion

The mean age of recipients in our study was 36.0 ± 1.1 years. Though this does not represent all the ESRD population of our hospital, this still reflects a relatively young age group of our ESRD patients. This is in contrast to developed countries where the elderly ESRD population is increasing.[8] Our study and other studies show that ESRD commonly affects people in their productive age group in Nepal. [9, 10]

The most common cause of ESRD in our study was Chronic Glomerulonephritis 44%, followed by hypertension 26% and Diabetes Mellitus 10%. This is in accordance with other studies which show similar etiologies of ESRD in the country. [9, 10]

70% of the donors in our cohort were genetically related. The present law of the country only allows potential renal transplant donors to be very close relative of the recipients, namely father, mother, brother, sister, husband, wife, son, daughter, uncle, aunt, mother in law, father in law, step father, step mother, and adopted son.[11] This has lead to a small number of donor pool, and is one of the factors hindering the further growth of renal transplant in the country. Cautiously liberalizing the present law to include potential donors from the maternal side and also the altruistic donors may help in expanding the donor pool. Besides, making ways for cadaveric transplant, ABO incompatible transplants and paired kidney exchange are the other solutions.

We preferred induction with ATG, 2 doses of 1mg/kg, in day 0 and day1, in all our recipients unless contraindicated either because of recent infections or financial constrains;

accordingly 74% of our recipients received ATG. Induction with ATG has shown to decrease the rate of acute rejections in first year post transplant. [12] In the literature the rate of acute rejection post transplantation is reported to be about 15-35 % depending upon the immunological risk and immunosuppressive regimens used. [13, 14] In our study we observed a relatively low rate of acute rejection, i.e. 12 %, in first three months post transplant. We did not compare the rate of acute rejections between the recipients who have or have not received ATG, as the total number of acute rejections in our study was quiet low and any differences, if any, would have been statistically insignificant.

All our recipients were initiated on Tacrolimus (TAC) + Mycophenolate Mofetil (MMF) + Steroid, as triple immunosuppressive regimen. We preferred TAC over Cyclosporin and MMF over Azathioprin, as the studies show better graft function, reduced rate of acute rejections, and better graft survival at 12 months. [15-18]

All the mortalities in our series were in elderly patients with co morbidities. The fatal incidents were two infections and one cardiovascular complication. The two infections were hospital acquired pneumonia following treatment of AMR in the post operative period, and community acquired pneumonia at the end of 3rd month. These infections taught us to be more aggressive in detecting and treating the infections in early post transplant period; indeed infections in the post transplant period are the common cause of morbidity and mortality in developing countries.[19] Cardiovascular complication was fall in blood pressure during the surgery in a recipient, who had diagnosed ischemic heart disease preoperatively, despite multiple inotropic drugs hypotension did not improve and he succumbed to death on 9th post operative day. Cardiovascular events account for the majority of deaths in the ESRD patients, and detailed cardiovascular assessment is a prerequisite before undergoing transplant surgery. In our transplant program, we routinely perform electrogardiography, chest x-ray and echocardiography by a cardiologist for all our potential transplant recipients. In addition we routinely perform pre transplant coronary angiography in all diabetic patients who are >50 years old. [7]

The most common non fatal infection in our study was Urinary Tract Infection (UTI), it occurred in 40 % of the recipients in first month and 10 % of the recipients in 1-3 months (a decreasing trend as days pass in the post transplant period). E. coli was the most commonly isolated organisms in UTI, 54 % and 33 % in first month and in 1-3 months, respectively. The other organisms isolated were Klebsiella pneumonia, Acinetobacter calcoaceticus baumanii complex, Pseudomonas aeruginosa, and Citrobacter freundii. The etiological spectrum of UTI in our study was similar to that reported in other studies.[20]

Besides UTIs and Pneumonias, other bacterial infections we encountered were one case each of epididymorchitis, and tubercular psoas abscess. The diagnosis of tubercular psoas abscess was made from the positive PCR (Polymerase Chain Reaction) of psoas abscess for tubercular bacilli.

We used universal prophylaxis with oral valgancyclovir in all our recipients for first 3 months, as all of our recipients and all of our donors were CMV IgG positive. We use 450 mg of oral valgancyclovir per day (half the recommended dose of 900 mg od), because of the cost issues and high incidences of leucopenia with standard dosing. Nevertheless we did not detect any case of CMV infection/disease, despite examining the suspected cases with Nucleic Acid Testing (NAT) during the episodes of febrile illness, pneumonitis and enteritis. We also did not detect any case of BK virus nephropathy in allograft biopsies performed in first three months.

We observed a low incidence of DGF (4%) in our study, and this is expected in live donor renal transplant.

The cumulative incidence of NODAT by the end of first year is generally found to be 10 -30 % in adults receiving Cyclosporin or Tacrolimus plus corticosteroid regimen.[21] NODAT occurred in 6 patients (12%) in our study.

Conclusion

The most common medical complication in first three months post transplant was urinary tract infection, followed by acute rejection, new onset diabetes mellitus after transplant and delayed graft function.

Conflict of interests: None Declared

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