Renal Transplantation - Calcutta Experience

Lt Col PP Varma^{*#}, Col Tapan Sinha⁺, Lt Col D Batura[#], Surg Cdr R Malik (Retd)^{**}
Lt Col RSV Kumar⁺⁺, Lt Col HS Gill^{##}, Col GS Chopra^{***}

Abstract

31 renal transplant procedures have been performed at this centre. Renal donors were father in 4, mother in 4, brother in 12, sister in 4, brother-in-law in 1 and wives in 6 cases. Median age of recipients and donors was 35.2 years (20-55) and 38.3 years (24-60) respectively. After a mean follow up of 15.7 months (2-40), graft survival was 96.7% and patient survival 90.3%. Three patients (9.6%) required surgical re-exploration, one each for, peri-graft haematoma, arterial kink and graft artery thrombosis. 6 patients (19.3%) required anti rejection therapy with resultant complete normalisation of graft functions. Medical complications noted were post transplant diabetes mellitus in 6 (19.3%), azathioprine induced bone marrow suppression in 1 (3.2%), tuberculosis in 2 (6.4%), post transplant erythrocytosis in 2 (6.4%) and recurrent urinary tract infection (UTI) in one (3.2%) patients. 3 patients (9.6%) died with functioning graft, one due to lung infection and the other due to haemorrhagic pancreatitis and third due to infective endocarditis.

MJAFI 2002; 58 : 196-200

Key Words: Post-transplant complications; Renal Transplantation.

Introduction

In India, renal transplantation started in the seventies and in the Armed Forces at present, renal transplantation is being done at Army Hospital (R&R), INHS Asvini, Command Hospital (Eastern Command), Kolkata and Command Hospital (Air Force), Bangalore. The arena of transplantation has seen sea changes over the last two decades as a result of pioneering researches in the fields of transplant immunology, HLA typing and better and safer immunosuppressives. Today in the western world many centres have achieved one year (short-term) graft survival of 95% [1,2]. Unlike the western world, where majority of kidneys come from cadavers, in India most of the transplants are living related. Command Hospital (Eastern Command) started the transplant program in 1998. This report is aimed at giving the preliminary experience of our centre.

Material and Methods

All patients accepted for transplantation satisfied the guidelines laid in Human Organ Transplant Act (HOTA), and were cleared by hospital ethical committee. After a general evaluation, to exclude donor risk, the donors were assessed for split renal functions of the kidneys and for suitability of vascular anastomosis. We preferred to harvest the renal unit with a single renal artery. The facilities of a comprehensive pre-transplant work up, including renal angiography, colour Doppler, HLA and cross match are available in the hospital. The selected kidney is harvested through the bed of 11th rib approach, taking care to preserve the peripelvic and periureteric tissues with the gonadal ves-

sels. After harvesting, the kidney is perfused on the bench with heparinised chilled Ringers lactate solution.

Donor kidney is conventionally placed in right iliac fossa of the recipient. The graft renal artery is anastomosed end to end with the recipient internal iliac artery and renal vein end to side with external iliac vein. Ureteroneocystostomy is done by the Lich Gregoir's extravesical method. We stent the ureter only if there is no urine flow after anastomosis or if the bladder wall is friable. HbsAg positive/anti HCV positive recipients are accepted only if there is no evidence of chronic hepatitis on liver biopsy. In the post-operative period, during the phase of diuresis, which lasts for 4-5 days, replacement fluid is normal saline and 5% glucose in equal amounts. Potassium supplementation is 120-180 meq/day till patient is taking liberal unrestricted oral fluids. Patients are kept on sulpha-trimethoprim combination for a period of three months, as prophylaxis for urinary tract infection (UTI) and *Pneumocystis carinii* infection. Urinary catheter was being removed initially by the 7th day but is now being removed by 5th post-operative day, and by this time drain is also out. Stitches are removed on 14th day by which time patient is fit for discharge.

Our immunosuppressive protocol involves three drugs- cyclosporin (CyA), azathioprine (Aza)/mycophenolate mofetil (Cellcept) and steroids, which are started a day prior to surgery. On D-1 day in place of oral steroids, recipients were given 15 mg/kg of intravenous methyl-prednisolone. Initial dosage of CyA, Aza and prednisolone (Pred) were 8, 1 and 0.15 mg/kg respectively. CyA was reduced by 1 mg/kg/per month and steroids by 2.5 mg every fortnight and by the end of three months most patients are on 5 mg/kg of CyA and on 10 mg steroids/day. Whole blood CyA levels, performed by HPLC method monitored the

^{*}Classified Specialist (Medicine & Nephrology), ^{***}Senior Adviser (Pathology and Transplant Immunology), Army Hospital (R&R), Delhi Cantt-110 010, ⁺Senior Adviser (Surgery & Urology), ⁺Classified Specialist (Surgery & Urology), Command Hospital, (Eastern Command), Kolkata, ⁺⁺Classified Specialist (Medicine and Nephrology) Command Hospital (Air Force) Bangalore, ^{**}Ex-Classified Specialist (Medicine & Nephrology).

dose of CyA. We maintained CyA levels between 250-300ng/ml during first 3 months, 200-250 ng/ml during next 3 months and around 200 ng/ml for next six months. After one year CyA levels were kept between 100-150 ng/ml and the drug was continued life long for unrelated transplants and for 2-3 years in related transplants.

Results

The centre has performed 31 transplants. Median age of donors was 35.2 (20-55) years. Donors were father in 4, mother in 4, brother in 12, sister in 4, brother-in-law in 1 and wife in 6 cases i.e. 24 cases (77.4%) received related and 7(22.5%) unrelated transplants.

Median age of recipients was 38.3 (24-60) years with 27 males and 4 females. 19 recipients were haplomatch with donors, one had full house match, 4 had two antigen matches, one had one antigen match and the rest 6 had zero matches. In one patient renal bed was made in left iliac fossa as he had clinical and Doppler evidence of right ilio-femoral vein narrowing. In 7 cases ureteric stents were placed. 2 patients had double renal artery requiring dual arterial anastomosis.

Graft and patient survival : One-year graft survival rate was 96.3%. Six patients (19.3%) were treated for acute cellular rejection episode; of these, 5 had biopsy proven acute cellular rejection. 6 patients were getting mycophenolate (Cya+Cellcept+Pred) while 25 were on conventional Aza (Cya+Aza+Pred). One patient from mycophenolate group(1/6) while 5 from Aza group (5/25) developed acute rejection. There was a trend of fewer rejections in mycophenolate arm, however, due to the small number, statistical significance is not achieved. All of them responded to pulse steroids with complete normalisation of renal functions. 3 patients expired, one, 4 months after transplant due to bilateral pneumonia, the other, 2 months after transplantation due to haemorrhagic pancreatitis and third 6 months after transplant due to infective endocarditis. These patients died with functional grafts. After a mean follow up of 13.4 months the serum creatinine was 1.5 mg/dl (0.9-2.0).

Fig. 1 : Patient and graft survival - year-wise

Surgical morbidity : 3 patients (9.6%) required re-exploration. One patient developed significant perigraft haematoma, resulting in hemodynamic compromise, which necessitated re-exploration on day of surgery. This patient had around 1 litre of haematoma from a drain site bleeder in the abdominal parieties and only required tying of a superficial bleeder. Another patient developed drop in urine output and accelerated hypertension on first post-operative day. A Doppler study suggested poor perfusion of the graft. On re-exploration, there was no thrombosis in the artery and graft was healthy. For a possible vessel kink leading to a subclinical distal thrombosis, parental anticoagulants were given. The patient subsequently made good recovery and was discharged six weeks later with serum creatinine of

EXP
10%

Fig. 2 : Patient survival (n=31), follow up = 15.7 m

Fig. 3 : Graft survival (n=31), follow up = 15.7 m

Fig. 4: Surgical morbidity (n=31)

1.8mg/dl. Third patient developed sudden cessation of urine 2 days after surgery. Doppler showed absent arterial flow suggesting graft artery thrombosis and patient required graft nephrectomy. We did not encounter any urine leaks, urinomas or lymphoceles in our patients.

Medical morbidity : 6 patients (19.3%) developed post transplant diabetes mellitus (PTDM) on an average 3 months (2-6), after transplantation. 3 of these required oral hypoglycaemic agents for 3 months only, while other 3 are still receiving drug 7,7 and 12 months after the transplantation. One (3.2%) developed reversible Aza induced bone marrow suppression, 6 months after transplantation, which lasted for a month after Aza withdrawal. He is continuing on two-drug immunosuppressive regimen with normal graft function. 2 patients (6.4%) developed pulmonary tuberculosis (TB), one developed pulmonary TB six months after transplantation and another TB lymphadenitis, 3 months after transplantation. We used ciprofloxacin in place of rifampicin in both our patients, both have completed therapy and are doing fine. 7 cases (22.5%) had positive urine culture immediately after catheter removal, however by 10th post operative day, 29 patients had sterile cultures. One patient required urinary antibiotics for a week while another continues to have recurrent UTI, despite initial antibiotic prophylaxis for 3 months. 2 patients developed erythrocytosis 3, and 4 months following transplantation respectively, which responded within 6 weeks of treatment with 2.5 mg of enalapril/day. 2 patients were HbsAg+ve, HbeAg+ve and anti HCV + ve before transplantation but their liver biopsy was normal. One of them expired due to pancreatitis and the other is maintaining normal liver functions 23 months after transplantation. One patient became HbsAg positive a month after transplantation and at liver biopsy the histology showed chronic hepatitis (score 5/20). He was started on lamivudine and is doing well. After 7 months of treatment his liver enzymes became normal and repeat liver biopsy showed regression of changes (1/20).

Fig. 5: Medical morbidity (n=31)

Discussion

Many transplant centres have reported one-year graft survival rate of 96-97% [2]. Our short term graft survival rate of 95% is comparable.

HOTA of 1994, passed by Parliament in 1995 has been adopted by most of the states. As per this act, a person can receive a kidney from his/her father, mother, brother, sister, son, daughter or spouse. Spousal transplant though only emotionally related, is permitted by the HOTA. Our centre is strictly adhering to this act. We had 19.3% spousal transplants, which are comparable to the rates reported in Indian series (22.5-23%) [4,5]. However, there is a rising trend towards spousal transplants in our country, raising fears of family pressures and compulsions being the reason for organ donation. We did not note such a trend in our data, which we believe is due to an elaborate counselling practice, involving as many members of the patient's family as possible. Interestingly, the results of spousal transplantation, as reported by most of the centres are superior to cadaveric transplantation though both have zero matching.

Graft artery thrombosis is reported between 0.5%-8% of renal transplant operations [6], develops usually on 2nd or 3rd postoperative day, though can develop upto 2 months later and is invariably a technical complication. Even if opened early graft is invariably lost. Graft artery thrombosis can also develop in setting of multiple renal arteries, in cyclosporin treated patients and in olden times it was a manifestation of hyperacute rejection [6].

PTDM is reported in upto 15% of patients and is the result of immunosuppressives, steroids being the biggest culprit. Most of the studies show that 50% patients remit after reduction in steroid dose while other 50% continue to require drugs [7]. Many workers in the western world are trying steroid free immunosuppressive protocols, either soon after the

transplant or a few months later. Though initial studies showed increased incidence of rejection after steroid withdrawal it appears that with newer immuno-suppressive drugs, mycophenolate and rapamycin this is possible [8,9]. These protocols are expected to reduce significant steroid related morbidity in these patients.

Aza induced bone marrow (BM) suppression is encountered in 10-15% patients [10] and is usually the result of cumulative dose of Aza. Most of the patients develop leucopenia while a minority develops isolated pure red cell aplasia. Stoppage/reduction in Aza dose usually results in recovery of bone marrow over 2-4 weeks. Use of granulocyte macrophage colony stimulating factor during this phase of leucopenia has proved rewarding, especially in a setting of infection [11]. Most of the centres in the western world have replaced Aza with mycophenolate mofetil in the immunosuppressive protocols.

In Indian scenario, TB is an important infection in these patients with an incidence of 10-12% [12]. Pulmonary form is the commonest followed by disseminated TB. Though, *Mycobacterium tuberculosis* is the commonest pathogen in India, atypical mycobacterial infection is quite common. Besides pulmonary lesions, these patients develop the disease at unusual sites e.g. skin, bones etc [13,14]. Duration of treatment in these patients is no different from other immunocompetent patients. One has to keep in mind that rifampicin by inducing the hepatic cytochrome 450 system, reduces the cyclosporin levels, warranting almost doubling of its dose and its frequent blood level monitoring. Erythrocytosis following transplantation develops in 10-15% patients and is the result of excess erythropoietin production by the native kidneys or other unidentified factors. ACE inhibitors or AT II receptor blockers have been found to be useful in over 90% of these patients [15].

Hepatitis B and hepatitis C virus infection are important causes of morbidity and mortality in renal transplant recipients. Present histological classification of chronic liver disease focuses on activity and fibrosis, which makes the future assessment/response to treatment, easier to quantify [16].

Newer available immunosuppressive drugs e.g. rapamycin and mycophenolate mofetil have reduced the acute rejection episodes and are big steps in prolonging graft survival. Simulect, an IL-2 receptor blocker given prophylactically has reduced rejection rates by 50%. A lot of work needs to be done in identification and control of non-immunological factors like disturbances in lipid profile, oxidant injury, hypertension etc. Today, thrust is in direction of invention of safer

drugs, which can prolong the graft life without producing harmful complications [17,18].

Initial 2-3 years are the learning phase of a centre, but with dedicated teamwork even during initial phase, results comparable to the best in the world can be achieved.

Acknowledgement

We express our profound gratitude towards Lt Gen SP Datta AVSM (Retd) who was the architect of this transplant program.

References

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Eng J Med* 2000;342:605-12.
2. Whelchel JD, Hymes LC, Hochgelerent EL, Larsen CP, Lowance DC, O'Brien DP et al. Evolving strategies in immuno-suppressive therapy : The Emory experience. *Clinical Transplants* 1996;249-55.
3. Pirsch JD . Long term management of immunosuppression in the renal transplant patient. *Current Opinion in Organ Transplantation*. 1997;2:78-81.
4. Bhowmik D, Dash SC, Tiwary SC et al. Changing trends in live related renal transplantation. *Proceedings of the XI Annual Conference of the Indian Society of Organ Transplantation*, 1999.
5. Singh P, Kumar A, Srivastava A et al. Kidney donations from wives : an exploitation or social compulsion. *Proceedings of the XI Annual Conference of the Indian Society of Organ Transplantation*, 1999.
6. Dodhia N, Rodby RA, Jensik SC, Korbet SM. Renal transplant arterial thrombosis : Association with cyclosporin. *Am J Kid Diseases* 1991;17:532-6.
7. Jindal RM. Transplant Diabetes Mellitus - A Review. *Transplantation* 1994;58:1289-98.
8. Dunn TB, Asolti M, Holman DM, Raofi V, Jovanovic B, Pollack R et al. Long term outcome of a prospective trial of steroid withdrawal after kidney transplantation. *Surgery* 1999;125:155-9.
9. Steroid Withdrawal Study Group. Prednisone Withdrawal in kidney transplant recipients on cyclosporin and mycophenolate mofetil - A prospective randomised study. *Transplantation* 1999;68:1865-74.
10. Varma PP, Prasher PK, Madan H, Yashpal. Azathioprine induced bone marrow suppression in live related renal allograft recipients. *MJAFI* 1996;52,1:45-7.
11. Narula AS, Chopra GS, Chaudary NR, Nair V, Kolhe VS. GM-CSF in a renal allograft recipient with Toxoplasmosis and leucopenia. *Ind J Nephrol* 1997;7:11-3.
12. Sakhuja V, Jha V, Varma PP, Joshi K, Chugh KS. The high incidence of tuberculosis among renal transplant recipients in India. *Transplantation* 1996;61,2:211-5.
13. Ghosh AK, Varma PP, Jha V, Gupta KL, Sakhuja V, Chugh KS. Disseminated tuberculosis in a renal transplant recipient presenting as a non-healing skin ulcer - A case report. *The Int*

J Art Organs 1993;6:132-4.

14. Sakhuja V, Varma PP, Kathuria P, Jha V, Chugh KS. Bone Tuberculosis : An unusual case of mycobacterial infection in a renal allograft recipient. Nephrol Dial Transplant 1993;8:868-70.
15. MacDugall IC. Role of angiotensin converting enzyme inhibitor and angiotensinogen II receptor blocker in the response to epotien. Nephrol Dial Transplantation 1999;14:1836-41.
16. Dienstag JL, Iselbacher KJ. Chronic Hepatitis. In : Harrison's principles of Internal Medicine. Fauci AS, Braunwald E, Iselbacher KJ et al, editors. 14th ed. 1998:1697-1704. McGraw Hills, New York.
17. Denton MD, Magee CC, Sayegh MH. Immunosuppressive strategies in transplantation. The Lancet 1999;353:1083-91.
18. Mattos AM, Olyaci AJ, Pharm D, Benett WM. Nephrotoxicity of Immunosuppressive drugs : Long term consequences and Challenges for the Future. Am J Kid Diseases 2000;35:333-46.

ATTENTION SUBSCRIBERS

Subscription rates revised from 01 Apr 02. The new subscription rates are :-

(i) Serving AMC officers
(Being received through AFMS(O))	- Rs. 300/- per year
(ii) Life Membership	- Rs. 1500/-
(iii) Annual subscription
(Individual)	- Rs. 300/-
(iv) Annual subscription
(Institutional)	- Rs. 500/-
(v) Annual Subscription
(Foreign countries)	- 120/- US \$

- Note
1. Please make your cheques or bank drafts in favour of Medical journal Armed Forces India, payable at Pune. For outstation cheques add Rs. 30/- as bank commission.
 2. Intimate non-reciept of issue within three months from the month of publication.