Renal Transplantation: Experience at a Single Centre

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Abstract

Background: Renal transplantation program in the Armed Forces commenced in Feb 1991 and till date 245 patients have undergone renal transplantation at INHS Asvini. We describe our protocols for donor and recipient evaluation and immunosuppression.

Methods: 245 patients received renal transplants during this period, 243 (99.2%) being from live donors. Most of them were started on triple immunosuppression comprising of cyclosporine, azathioprine and prednisolone. Newer drugs like mycophenolate, tacrolimus and sirolimus were administered in a select population.

Result: 69 (28.1%) of them had at least one episode of acute rejection, most of which were steroid responsive and 13 (18.8%) of them required either anti CD3 monoclonal or anti-thymocyte globulin (ATG). Complete recovery with normal renal function occurred in 54 (78.2%) cases and 15 (21.7%) recovered with residual dysfunction with maximum serum creatinine being 2.1mg/dl. There were three (1.2%) cases of accelerated rejection during the first week of transplantation and one had graft rupture. All three lost their grafts. There were eight (3.2%) cases of acute tubular necrosis, who recovered completely within 8-14 days. Immediate infections included wound sepsis, lower respiratory tract infection, disseminated candidiasis and disseminated aspergillosis. Late infections included pulmonary tuberculosis, disseminated tuberculosis, cytomegalovirus infection and recurrent urinary tract infection. 28 (11.4%) patients developed post transplant diabetes mellitus. At the end of one year and five years, graft and patient survival were 97.2%, 93%, 80.9% and 85.7% respectively.

Conclusion: Our outcomes show that the transplantation is a viable mode of renal replacement therapy in patients of end stage kidney disease with a near normal rehabilitation.

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Key Words : Kidney; Transplantation; Immunosuppression; Complications

Introduction

Renal transplantation has emerged as the treatment of choice for patients of end stage renal disease (ESRD). Live related renal transplantation is being done in our country regularly for last three decades. However the first renal transplantation in an Armed Forces Hospital was done on 11 Feb 1991 at this hospital and since then 245 transplantations have been carried out. We present our experience of renal transplantation at INHS Asvini and our protocols for donor and recipient evaluation and immunosuppression.

Material and Methods

A total of 245 renal transplants have been performed from 1991 to 2007 at our hospital. There were 205 males and 40 females in the age range of 10 to 61 years. The year wise transplant data is as shown in Fig. 1.

The etiology of ESRD in the recipients was varied and the commonest cause was chronic glomerulonephritis seen in 149 (60.8%) patients. Etiological diagnosis was presumptive in most cases, the details of which are given in Table 1. All the patients were ascertained to be free from any medical, surgical or psychosocial factors that could be a contraindication for

renal transplantation. Evaluation included cardiac status, infection with any blood borne hepatotropic virus, liver biopsy in selected cases of chronic hepatitis, anatomical abnormality in native kidney (both congenital, like vesico ureteric reflux and acquired, like nephrolithiasis). All urological diseases were corrected prior to transplantation. All the patients were evaluated for occult dental and ear nose throat infections, tuberculosis, peptic ulcer disease, gall bladder disease and other organ involvement. Most of our

Total Transplants Up to 2007= 245

Fig. 1 : Yearly transplant data

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Table 1**Causes of renal failure**

Chronic glomerulonephritis	149 (60.8%)
Benign nephrosclerosis	31 (12.65%)
Chronic interstitial nephritis	30 (12.24%)
Diabetic nephropathy	11 (4.48%)
Autosomal dominant polycystic kidney disease	07 (2.85%)
Graft failure	04 (1.63%)
Vesico-ureteric reflux	09 (7.75%)
Systemic lupus erythematosus	01 (0.4%)
IgA nephropathy	01 (0.4%)
Renal tuberculosis	01 (0.4%)
Rapidly progressive glomerulonephritis	01 (0.4%)

patients were already been exposed to tuberculosis and cytomegalo virus (CMV) and hence prophylaxis against these diseases was not contemplated.

Only two of the transplants were from deceased donors and the rest were from live donors. All the live donations were emotionally related and altruistic and were in accordance with Human Organ Transplantation Act 1991. 171 of them were biologically related including parents, siblings, children, first degree cousins, uncle, aunt and nephew and 72 were not biologically related, of which 60 were spouses (Fig 2). There were 17 HLA identical donors and 78 were HLA haplo identical. There were two cadaver organs which were mismatched for all antigens.

Immunosuppressive protocols did not change much during the last 16 years. Triple drug therapy with cyclosporine, azathioprine and prednisolone was commonly used along with injection methyl prednisolone 500mg on day -1 and day 0 and 250 mg on day +1 and day +2. Cyclosporine was started at a dose of 8mg/kg on day -2 and azathioprine at a dose of 1-1.5 mg/kg along with prednisolone at a dose of 0.5 mg/kg per day from day+3. Cyclosporine level at trough (Co) was measured on day 5 and the dosage adjustment was done to keep the level between 250-375 ng/ml for six months and between 100-250 ng/ml after six months.

Mycophenolate mofetil (MMF) was introduced into our regimen in 2001 in place of azathioprine and 40 (16.3%) were put on MMF, mostly patients who were thought to be relatively of higher immunogenicity. In addition MMF has been introduced in 37 patients during their follow up mostly for chronic allograft nephropathy. IL-2 receptor blockers (Simulect & Zenapax) have been in use since 2000 and have been used in 54 (22%) patients during the induction phase in selected patients- children, diabetics, re-transplants, biologically unrelated and mismatched transplants.

Acute rejection was diagnosed whenever there was a sudden deterioration of the graft function with an increment of at least 25% of serum creatinine as compared to baseline levels. All these patients were treated with Injection methyl prednisolone 250-500 mg intravenously on three consecutive days.

Results

Two hundred and forty five patients received a renal

Table 2**Early fatal complications**

Septicemia with wound sepsis	05 (2%)
Septicemia with pneumonia	03 (1.2%)
Disseminated candidiasis	01 (0.4%)
Disseminated aspergillosis	01 (0.4%)
Graft rupture	01 (0.4%)
Acute myocardial infarction	01 (0.4%)
Unknown	01 (0.4%)
Total	13 (5.6%)

Fig. 2 : Donor relationship profile

allograft at INHS Asvini between Feb 1991 and Aug 2007 as shown in Fig.1. Most of the recipients were male - 205 (83.6%) in the range of 10-61 years and females numbered 40 (16.3%) in the range of 16-46 years. The donors were mostly female- 139 (56.7%) and males numbered 104 (42.4%). Two (0.8%) organs were harvested from deceased donors. Mean age of donors was 36 ± 2.4 years (range 26-64 years). One hundred and seventy one (70.3%) were genetically related and 72 (24.6%) were genetically unrelated (Fig. 2).

Most of the recipients were on follow up for at least five years and were encouraged to send us a post card at least once a year on the anniversary of their transplantation. Forty-six (18.7%) of the patients could not be traced and were lost to follow up. There were 13 fatalities during the first month of transplantation (Table 2). Immediate non-fatal complications have been enumerated in Table 3. Thirteen patients had various surgical complications and 85 patients had medical complications. Only 5 (2%) patients had UTI during the period. At the end of the year, the graft and patient survival were 97.2 and 93% respectively. One hundred and sixty eight (68.5%) patients have completed at least five years post transplant period. The number with functioning graft at the end of five years is 136 (80.9%) and the number of surviving patients is 144 (85.7%). Sixty-nine (41.0%) patients have completed 10 years post transplant period.

There were three cases (1.2%) of accelerated rejection during first week of transplant and the grafts could not be salvaged. In the immediate post transplant period, 69 (28.1%) patients had acute rejection, which was treated with steroids, of which 13 (18.8%) patients did not respond to steroids. The

Table 3**Early non-fatal complications**

Acute rejection	69 (27.6%)
Acute tubular necrosis	08 (3.2%)
Urinary tract infection	05 (2.0%)
Wound dehiscence	05 (2.0%)
Urine leak	04 (1.6%)
Accelerated rejection	03 (1.2%)
Disseminated varicella	02 (0.8%)
Renal vein thrombosis	01 (0.4%)
Lymphocele	01 (0.4%)
Chylocele	01 (0.4%)
Graft artery thrombosis	01 (0.4%)

diagnosis was confirmed histologically in all prior to treatment with monoclonal antibodies (10 cases) and ATG (3 cases). There were 8 (3.2%) cases of acute tubular necrosis, which recovered with conservative management.

During long term follow up, 28 (11.4%) patients developed post transplant diabetes mellitus. Infections included pulmonary tuberculosis in seven (2.8%), disseminated tuberculosis in two (0.8%), CMV in seven (2.8%), recurrent urinary tract infection (UTI) in two (0.8%), disseminated aspergillosis in one and cryptococcal pneumonia in one (Table 4). There were 16 (6.5%) patients who developed leucopenia over a variable period of time which recovered after dosage reduction or withdrawal of azathioprine. 15 (6.1%) developed erythrocytosis and were mostly managed with angiotensin converting enzyme inhibitor (ACEI). Eight (3.6%) patients developed acute pancreatitis and all of them responded to conservative management.

There were a total of 26 (10.4%) patients with chronic hepatitis B infection who received renal allograft. There has been no case of chronic HBV infection since Dec 2003. Hepatitis C virus monitoring is being done regularly since 1999 and 18 (7.2%) cases of chronic HCV infection have been transplanted so far. Six (33%) of these 18 cases of chronic HCV infection developed new onset diabetes mellitus.

Discussion

Renal transplantation as a mode of therapy for ESRD is an excellent and viable modality of therapy. The bottleneck for universal implementation of this therapy has always been the availability of donors. Since cadaver transplantation in this country has not really been established, only two (0.8%) of the transplants have been deceased donor organs.

Even though Human Organ Transplant Act 1991 was promulgated to give fillip to deceased donor transplant program in the country more than 99% of all transplants in the country still happen to be from live donors. However, live donor transplantation provides a better patient and graft survival as compared to deceased donor transplantation [1], because the quality of donor kidneys can be selected prior to the transplantation. The deceased donor transplantation has less delayed graft

Table 4**Long term complications**

Post transplant diabetes mellitus	28 (11.2%)
Leucopenia	16 (6.4%)
Post transplant erythrocytosis	15 (6.0%)
Acute pancreatitis	08 (3.2%)
Pulmonary tuberculosis	07 (2.8%)
Cytomegalo virus disease	04 (1.6%)
Disseminated tuberculosis	02 (0.8%)
Recurrent UTI	02 (0.8%)
Malignancies (carcinoma esophagus and acute lymphoblastic leukemia one each)	02 (0.8%)

function during the immediate post transplant period due to reduced warm and cold ischemia times. In countries where deceased donor transplantation was prevalent earlier, the number of living donor transplantation is increasing in view of its better results. In USA, the annual number of live kidney donors has surpassed the number of deceased donors since 2001 [2].

Most (83.6%) of our patients were males, whereas the donors were predominantly (56.7 %) females. In United States too, 60% of live donor population has been females [2]. This pattern is similar to what has been observed worldwide, with more male recipients undergoing live donor transplantation [1].

Majority of the donors were genetically related constituting 70.4% of study population. 29.6% of all our live donors were genetically unrelated, predominantly the spouse (83.3%) and wife donating 88.3% of the time. The rest 16.7% of the live unrelated donors (LURD) have been other family members. The LURD is not being discouraged worldwide, in view of the excellent five-year results as seen in UNOS Transplant registry [3]. With our immunosuppression protocol, the outcome of a kidney transplant from a completely mismatched donor is no different from that of a haplo-identical match [2].

Until 1978, azathioprine and steroids were used as primary immunosuppressive agents and resulted in an 50-60% incidence of acute rejections, with a short time graft survival of 60%. With introduction of cyclosporine there was a significant decrease in number of grafts lost due to acute rejections and the incidence of acute rejections reduced to 30% [4,5]. Initially cyclosporine was used in very high dose with significant nephrotoxicity. However to maintain improved immunosuppression provided by cyclosporine and to reduce its side effects, triple therapy was introduced in 1985 [6,7]. The results of this therapy were excellent and in a deceased donor setting, one year graft survival was around 80% with substantial number being rejection free [8]. Attempts have been made to omit either azathioprine or steroids in many studies [9]. Of the patients whose steroids were

omitted, 36% required high dose steroid therapy for reversal of rejections, thus compromising any benefit of steroid sparing [10]. From the beginning, our protocol consisted of standard triple immunosuppression. 28.1% have developed acute rejections and 81.2% of them responded to a 3-5 day course of injection methyl prednisolone. 18.8% of these rejections were steroid resistant and they were treated with either monoclonal antibodies to CD3 or anti-thymocyte globulin (ATG). 1.2% developed acute vascular rejection and lost their grafts.

The use of humanized or chimeric monoclonal antibodies against the IL-2 receptor has resulted in decreased incidence of rejection without an apparent increase in infection or lymphoproliferative disease [11, 12] as compared with anti lymphocyte globulin or anti thymocyte globulin. These drugs have been used in patients who have a higher chances of acute rejection like poorly matched patients and children. We did not find any significant difference in incidence of rejection with or without use, probably because of selection bias.

Of late, mycophenolate mofetil (MMF) has been in use in place of azathioprine. In pooled analysis of three land mark trials [13-15], MMF significantly reduced the incidence of biopsy proven rejection episodes in the first year after transplantation from 40% for placebo/azathioprine patients to 19.8% for MMF 2 gm/day and to 16.5% for MMF 3gm /day. An increase in tissue invasive cytomegalovirus disease has been seen in MMF treated patients (2gm/day-8.3% and 3gm/day 11.5%) compared with azathioprine treated patients (6.1%) [16]. However, MMF has not been shown to have a significant difference in graft survival and it has led to considerable uncertainty about the place of MMF in immunosuppressive therapy. Though all large studies have continued MMF indefinitely, the major clinical advantage appears to be in the first three months. Withdrawal of MMF at 3-6 months with introduction of azathioprine needs to be reviewed [17].

In the setting of immunosuppressed state due to ESRD, the transplant surgery itself increases the risk of infections. The principal factors determining the type and severity of infections are the intensity of exposure to potential pathogens and overall state of immunosuppression [18]. A total of 13 (5.6%) patients had varying life threatening infections during the first three months of transplantation and another 12 (4.8%) had non serious infections including UTI (2%) and recurrent UTI (0.8%) during the period. However, in a prospective study 20.8% were shown to have UTI during the first three months of renal transplantation [19]. Our pick up rate of UTI seems to be much lower than reported and it may be worthwhile looking for infection

in the urinary tract more pro-actively.

Tuberculosis was diagnosed in nine (3.6%) of cases in our patients, whereas in a prospective analysis of 266 patients, 17% had tuberculosis [19]. Disseminated varicella occurred in two (0.8%) patients during the first month of transplantation, one of them associated with acute pancreatitis, hepatitis and subsequent acute graft dysfunction. Twenty six (10.2%) of our patients were suffering from chronic hepatitis B infection and 18 (7.2%) with hepatitis C virus infection at the time of transplantation. Even though certain authors have shown lower survival in HCV infected recipients [20], our HCV positive patients did no differently from other patients. Australia-New Zealand Dialysis and Transplantation Registry (ANZDATA) shows that the overall incidence of cancer in renal transplant recipient is greater than in patients on dialysis and general population [21]. However only two (0.8%) of our cases had presented with malignancies; one as acute lymphoblastic leukemia and other as carcinoma esophagus, three months and four years after transplantation. Both these cases are probably not “transplant-associated”. The most common malignancies in these patients are central nervous system lymphoma, Kaposi sarcoma, carcinoma uterine cervix and carcinoma of vulva [21].

This report is a summary of our clientele, donor profile, and various immunosuppressive protocols, problems and complications encountered during the course of their management. Our outcomes show that transplantation is a viable mode of renal replacement therapy in patients of end stage kidney disease with a near normal rehabilitation.

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Conflicts of Interest

None identified

Intellectual Contribution of Authors

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