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Original Article

Pre-emptive live-donor kidney transplantation: Clinical course and outcome

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Abstract

Background/Aims: Renal transplantation (RTX) is a definitive therapeutic modality in end-stage renal disease (ESRD).Most ESRD patients in Egypt experience dialysis prior to RTX. Dialysis is not only associated with morbidity, but it is also expensive. In developing countries, pre-emptive transplantation (PTX) may be a cost-effective option, offering an additional benefit to conventional RTx.

Materials: Between March 1976 and March 2001, 1279 first live-related transplants performed in our center. The 82 (6.4%) patients transplanted without prior dialysis were compared with 1197 patients who had been dialyzed prior to transplantation.

Results: Median follow-up was 65.3 months in the PTX group and 62.1 months in the dialysis dependent control group. Dialysis dependent group received more blood transfusions (65% vs 30%) and, positive hepatitis B antigen positivity in 0.9%, while none of PTX group was HBsAg. The actuarial graft and patient survival at 5 years was comparable in both groups. (p= 0.2, 0.8 respectively). The incidence of acute and chronic rejection was not different between the two groups, Mortality rate was not different between both groups (20.7% vs 19.2% respectively), however, the incidence of cardiovascular causes of death with function graft in PTX group was significantly higher (37% vs 17%), while chronic liver disease leading to death was significantly higher in the control group (8% vs 0%).

Conclusion: PTX offers comparable patient and graft survival to conventional RTX. It eliminates the complications and inconvenience of dialysis. PTX is more cost-effective, therefore, it should be encouraged in a developing country.

Key words: Kidney; living; preemptive; transplantation

Introduction

Renal replacement therapy in developing countries is strongly influenced by economic factors. Maintenance dialysis, either hemodialysis or peritoneal dialysis, is expensive [1]. Renal transplantation is widely accepted as the treatment of choice for the majority of patients with ESRD requiring renal replacement therapy. Conventional management is to establish patients with ESRD on chronic dialysis and then consider them for inclusion in transplant program.

Pre-emptive renal transplantation (PTX) has the potential to avoid the morbidity of dialysis together with its financial costs and also maximizes the chance of maintaining a high quality of life. These benefits, however, must be offset by several potential disadvantages, including the possibility of transplantation many months before the need for dialysis, an immediate risk of graft failure with conversion to a dialysis- dependent state, and uncertainty of the safety of PTX [2,3]. The safety of PTX has been studied by different groups. Earlier clinical studies had suggested impaired patient and graft survival results in pre-emptive renal transplants [4]. More recent studies, however, were unable to confirm these findings [2,5-11]. On the contrary, an even better survival rates were reported [12-17].

The purpose of this study was to compare the results of conventional live-donor renal transplantation with pre-emptive renal transplantation to establish whether or not PTX could be justified on the basis of clinical outcome and also to study the financial concerns of PTX in our developing country.

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Material and methods

Patients: Between March 1976 and March 2001, 1279 patients received their primary renal allograft from living donor in our center.

Among them PTX was performed in patients with chronic renal failure before their need for chronic dialysis. These patients were selected for a retrospective analysis. All the remaining recipients who have been maintained on chronic hemodialysis before transplantation were considered as control group. A minimum follow-up of at least one year was present in all the patients.

Treatment: Patients were managed according to the standard center immunosuppressive protocols at subsequent eras. Before 1983, all patients received immunosuppression with azathioprine (Aza) in a dose of 2-3 mg/kg/day, and prednisolone (Pred) in a dose of 2mg/kg/day with subsequent tapering of the dose till 0.5mg/kg/day after one month. After 1983, other protocols have evolved over time. Cyclosporine (CsA) was introduced with two main protocols; CsA (12mg/kg/day) and Pred; or triple therapy in the form of CsA (10mg/kg/day), Pred and Aza (1mg/kg/day). CsA dose was adjusted to keep CsA trough level between 200-400 ng/ml in the first two months and between 125-175 thereafter. CsA trough level was measured at first using Radio Immunoassay Kits: Sandoz-Basel, Switzerland and then using monoclonal specific antibodies; Abbott Diagnostics TDx, USA. In 1990s, Tacrolimus (TAC) in a dose of 0.15mg/kg/day and/or Mycophenolate Mofetil (MMF) in a dose of 2gm/day were introduced as rescue therapy in some cases or to replace either CsA or Aza as a result of their side effects. TAC dose was adjusted to achieve a trough level of 5-10 ng/ml using MIA technique: Abbott Diagnostics IMX, USA.

Acute rejection episodes were treated by giving methyl prednisolone pulses (750mg/day for pred - Aza group and 500 mg/day for CsA - treated or FK - treated group). Pulses were given for 5 days and then tapered to the basal maintenance Pred dose at that time. Biopsy - proven steroid resistant rejection were treated with antithymocyte globulin (ATG, Fresenius) or OKT3 (Orthoclone). In cases with severe vascular rejection, plasma exchange was added to anti-rejection regimen.

Since June 1998, patients have received induction therapy in the form of basiliximab (Simulect, Novartis), daclizumab (Zenapax, Roche) or ATG according to protocol at that time. Secondary and tertiary immunosuppression were defined, respectively, as the first and second modification of maintenance (primary) immunosuppression protocol due to either the need to increase the level of immunosuppression or due to toxicity.

Follow up: Patients were closely monitored at the center for the first one year, then at intervals of one month for 5 years, and 3 monthly thereafter. Follow up data were obtained for all patients and all medical or surgical complications were recorded.

Outcomes: Graft failure was defined as the date of return to chronic dialysis or death with a functioning graft. Secondary outcome measures were number and timing of anti rejection treatments and serum creatinine recorded yearly at one year till 5 years and at the last follow up.

Results

At the Urology and Nephrology Center, Mansoura Egypt, 82 transplants were performed between March 1976 and March 2001 in which the criteria for PTX were fulfilled. Within the same period the center performed a total of 1179 first living renal transplants on dialysis-dependent individuals who were considered as control group.

Demographic characteristics: The distribution of PTX with respect to dialysis-dependent transplant along intervals (5 years) was illustrated in figure 1. Both groups were comparable regarding donor and recipient age and sex, original kidney disease, consanguinity, blood group, HLA typing, ischemia time and time to diuresis (table 1). However, the distribution of age in both groups demonstrated higher percent (18.5% vs 9.3%) of patients above 40 years in dialysis dependent group. Only pre-emptive patients (23%) were positive for HCV before transplant compared with patients (63%) control patients (P=0.00). In contrast to (12%) control patients (0.9%) who were positive HBs Ag before transplants, no one in the pre-emptive group was positive HBs Ag (P=0.00).

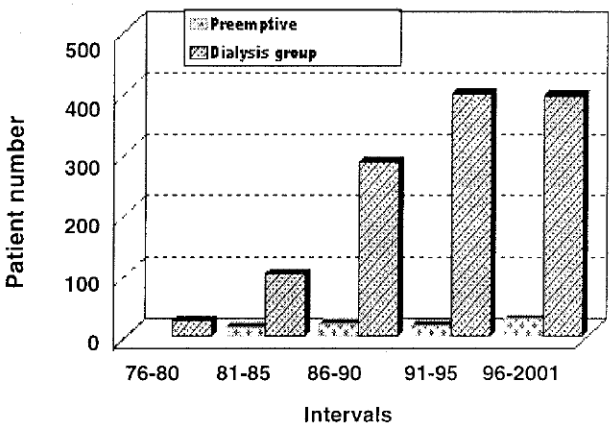

Fig. 1. The distribution of transplant over 5-years intervals

Table 1. Characteristics of patients pre-emptive versus dialysis groups

Characteristics	*Pre-emptive group (n= 82)*	*Dialysis group (n= 1197)*	*P*
Recipient age (M±SD)	27.9 ± 10.1	29.9 ± 10.3	0.09
Recipient sex, male/female(%)	63 / 37	76 / 24	0.02
Original kidney disease,	11/22/9/58	11/18/10/61	0.8

Glomerular/others/unknown (%)			
Donor age, (M±SD)	36.6±11.8	35.2±9.9	0.21
Donor sex, male/female (%)	56 / 44	48 / 52	0.14
Consanguinity (related/unrelated)	74 / 8	997 / 200	0.1
Blood group 65 / 17	961 / 236	0.8	
(same/different compatible)			
HLA' 0/1/2/3/4/5/6 mismatches (%)	4/1/10/71/5/9	8/1/12/55/15/9	0.1
Ischaemia time (minutes)	41.8±8.8	43.3±12.4	0.27
Time to diuresis immediate/delayed(%) 94 / 6	91 / 9	0.4	
Pretransplant transfusions			
Yes (%)	30	65	0.000
Number			0.000
(1-2/3-4/>4),%	33/42/25	29/30/41	
(1-3/4-5/>5), no.	18/2/4	360/156/236	0.000
> 10	1	43	

Control patients were more likely to have received blood transfusions before transplantations (30% vs 65%, P= 0.000). In the pre-emptive group, the majority (18/24, 75%) of those who had been transfused had received less than 4 units, in the main as a consequence of protocol transfusions and only one patient had received 10 units or more, whereas among the dialysis-dependent controls only 360/752 (47.9%), had received less than 4 units and 43 patients had received 10 units or more (P= 0.0001). Differences were not apparent between the two groups with respect to induction and maintenance immunosuppressive protocols (table 2). More than 75% of patients in both groups received CsA-based immunosuppressive protocols.

Table 2. Immunosuppressive protocol

	Pre-emptive group (n= 82) %	*Dialysis group (n= 1197)* %	*P*
Induction therapy	5	10	0.5
Primary immunosuppression			
Conventional	23	23	
CSA-based	77	76	0.8
FK-based	-	1	
Secondary immunosuppression	50	46	0.5
Tertiary immunosuppression	17	10	0.6

Outcomes: The mean follow-up was 77.6 ±61.7 months in the pre-emptive group and 69.3±63.9 months in the dialysis dependent group (P= 0.3). The morbidity illness after transplantation was comparable in the two groups (table 3).

Table 3. Post-transplant complications

	Pre-emptive group (n= 82) %	*Dialysis group (n= 1197)* %	*P*
Acute rejection			
Number (0/1/2/3/4)	39/40/15/6/43	36/13/6/2	0.7
Severity (cellular/vascular)	90 / 10	89 / 11	1.0
Response to treatment			
Responsive/resistant	83 / 17	83 / 17	1.0
Chronic allograft nephropathy	22	29	0.4
Medical complications			
Hypertension	71	75	0.6
Diabetes mellitus	13	14	0.9
Hepatic	6	9	0.7
Medical infections	22	30	0.3
Malignancy	2	4	0.8
Gastrointestinal	6	9	0.9
ATN	2.4	5	0.6
Surgical complications			
Surgical infection	0	1	0.7
Bleeding	3.7	2	0.2

Hypertension was present in more than 70% of patients in both groups. Hepatic dysfunction was noted to be more frequent in the dialysis-dependent group versus the pre-emptive group (9% vs 6%). However, this didn't rank to statistical significance (P= 0.7).

There were no significant differences with respect to the number of acute rejection episodes, severity and response to treatment. Fewer grafts failed within the first 3 months in the pre-emptive group, but this difference did not reach statistical significance (1/82 vs 27 / 1197, P= 0.1). The majority of early graft losses were the end result of uncontrolled rejection and there did not appear to be any difference between the groups with respect to the cause of graft failure. Late graft loss, more than 3 months after transplantation, was also less frequent in the pre-emptive group, but again this did not rank to statistical significance (22/82 vs 83/1197, P= 0.3). Of the 27 grafts lost in the pre-emptive group and 441 in the control group, chronic rejection accounted for the loss of 16 and 314 graft, respectively (P= 0.1).

Function of the surviving grafts: There was no significant difference in the function of the surviving grafts as determined by yearly serum creatinine measurements up to five years after transplantation (figure 2). Serum creatinine values (mean ± SD) at 1,2,3,4 and 5 years were 1.4±0.6, 1.6 ±0.7, 1.8±1.1, 1.8±1.1 and 1.9±1.1 versus 1.4±0.5, 1.6±0.8, 1.7±0.9, 1.8±1 and 1.8±1.1mg/dL for pre-emptive and controls respectively (P= >0.05).

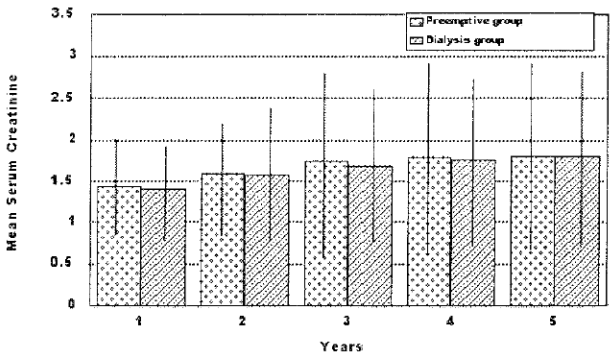

Fig. 2. Mean serum creatinine values (mg/dl) in both groups.

Actuarial graft survival rates (figure 3) were 93.8% and 81.2% at 1 and 5 years, respectively, in the pre-emptive group with 91.9% and 74.4%, respectively, in the dialysis-dependent group (P=0.2, 95% confidence interval= 9.9-14.2). Patient survival rates (figure 4) were 95.1% and 87.9% at 1 and 5 years, respectively, in the pre-emptive group and were comparable to the dialysis-dependent group; 95.7% and 87.9%, respectively (P= 0.8 and 95% confidence interval= 13.9-16.1).

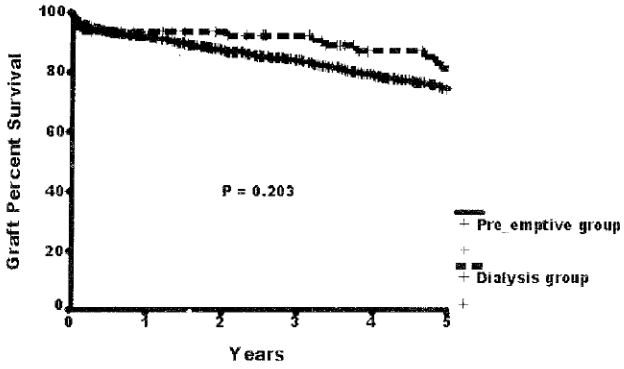

Fig. 3. Actuarial graft survival in both groups.

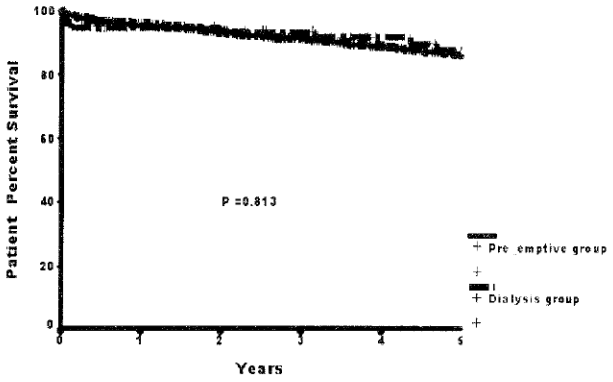

Fig. 4. Actuarial patient survival in both groups.

The overall patient and graft outcome were summarized in table 4. More than 60% of patients in both groups have functioning graft at last follow up.

Table 4. Causes of patients' deaths

	Died with function graft		*Died with failed graft*	
	Pre-emptive group %	Dialysis group %	Pre-emptive group %	Dialysis group %
Infections 9	8	0	7	
Cardiovascular	37	17	33	33
Hepatic	9	11	0	8
Gastrointestinal	9	6	0	2
Cerebrovascular	9	9	0	2
Malignancy 0	7	0	4	
Respiratory 9	22	17	10	
Bleeding 0	2	0	0	
Trauma	0	1	0	0
Others	9	0	0	0
Unknown 9	17	50	34	
P value	*0.03*	*1.0*		

The design of our study did not allow us to specifically examine the question of non compliance with immunosuppressive medications, but lack of significant late graft loss in the pre-emptive transplants suggests that this was a substantial problem. We have not been aware of any overt differences in compliance between the two groups.

Patient deaths: Patient deaths numbered 17/82 of the pre-emptive cohort and 230/1197 of the dialysis dependent (P = 0.9). An analysis of the causes of death is given in table 5. More than 50% of patients died with functioning grafts in both groups, however, this figure is higher in the pre-emptive group (11/17) versus in the dialysis dependent group (116/230). The cause of death with functioning graft were statistically significantly different between both groups (P= 0.03). Cardiovascular causes was the most common cause of death in the pre-emptive group (37%) while the respiratory tract infections and malignancy were the most prevalent in the control group (22% and 9% respectively). In patients who died with failed grafts, there was no significant differences in the causes of death between the two groups (P=1.0).

Table 5. Overall patient and graft outcomes

	Pre-emptive group (n= 82) %	Dialysis group (n= 1197) %	P
Living with functioning graft	67.1	63.2	
Living with failed graft	12.2	17.6	0.4
Died with functioning graft	13.4	9.7	
Died on dialysis	7.3	9.5	

Discussion

The main treatment option for ESRD patients is entry into a dialysis program until renal transplantation. Because the cost of dialysis is a source of great concern in developing countries and a factor limiting treatment, the substantial cost reduction brought about by PTX is of major importance [7]. In Egypt, the costs of haemodialysis for one year is $3100 per patient including the cost of thrice weekly haemodialysis, vascular access and transfusions, expenses for haemodialysis or access-related morbidity and/or hospitalization would be additional. On the other hand, the annual cost of transplantation is $3500 in the first year (including transplantation surgery) and then $1700 thereafter. Hence, transplantation is less costly than haemodialysis. Preemptive transplantation offers additional annual cost reduction of $3000-3500 pre-transplant haemodialysis cost than conventional transplantation.

In line with the group study of Papalois et al [16] the analysis of demographic characteristics of the recipients in the current study demonstrated that there was a trend to younger age distribution in the PTX. Otherwise, characteristics that could possibly affect the outcome (recipient and donor sex and age, HLA mismatch, original kidney disease), were similar for both pre emptive and control groups.

Until the mid-1980s, the general feeling was that PTX had inferior results compared with post dialysis transplantation [19,20]. In previous studies of PTX, involving both living and cadaver donors [5,8] and those involving only living donors [10,18], patients and graft survival rates were comparable between those undergoing pre-emptive renal transplantation and those who have been transplanted after a period of dialysis, while on another study involving living donors [16] better survival rates were observed in pre-emptive transplant patients. The study by Katz et al [5] of 85 pre-emptive transplants showed that both patient and graft survival rates were not different from control group. Of 132 pre-emptive transplants between 1968 and 1984, Migliori et al. [8] found that those from living donors performed as well as controls with respect to patient and graft survival. John et al. [10] reported that transplantation without dialysis was safe and successful and it could eliminate the complications and inconvenience of dialysis. Papalois et al. [16] observed that pre-emptively transplanted living renal grafts performed significantly better than patients who transplanted after dialysis. In our study group of living donor transplants, patient and graft survival rates were comparable between both groups in the short and long term. There were no significant differences in any measures of outcome analyzed (serum creatinine at yearly intervals, acute rejection frequency, severity, or response to treatment or prophylaxis. In our experience, the incidence of chronic rejection was also similar for pre emptive and dialysis dependent transplants. Our data indicate that the use of modern immunosuppressive therapy eliminates any potential risk for pre-emptively transplanted grafts that results from lack of uremia and blood transfusions in dialysis dependent patients.

In at least two other series [5,17] non compliance with immunosuppression was thought to have contributed to a high rate of acute rejection episodes in the pre-emptive transplants, but in our study, we have no evidence to suggest that, non compliance was more common after pre-emptive transplantation than after conventional transplantation. In the cyclosporin era, monitoring of drug levels regularly could be a marker of poor drug compliance.

HBsAg-positive patients undergoing renal transplantation have a less favorable outcome after allografting [21]. Post transplant hepatic disease has been associated with increased morbidity and mortality [22]. HBs Ag transmission with blood transfusion still is possible even with routine screening tests done for these

donors. Avoidance of multiple blood transfusions and dialytic procedure could help decrease the prevalence of HBs Ag positivity and liver disease after transplant. In our patients, we had no HBs Ag positive patients in the pre-emptive group. Chronic liver disease was responsible for 8% of long-term patients' deaths in the dialysis dependent group. Other than increasing morbidity, the onset of hepatic dysfunction delays renal transplantation, increasing the cost of dialysis.

Contrary to other studies [17] who found no deaths caused by sepsis or cardiac events for pre-emptive recipients, our current study demonstrates a higher rate of cardiovascular events in the pre-emptive recipients who died with functioning grafts and higher rate of infections and chronic liver disease leading to death in the dialysis dependent patients. The explanation for these findings is probably that more risky patients were selected for PTX and the fact that the morbidity in these risky patients increases on starting dialysis program before RTx.

In conclusion, this study appears to establish that pre-emptive renal transplantation is as safe as conventional transplantation with comparable graft and patient survival rates, and it may be an appropriate form of renal replacement therapy in a developing country. It minimizes the complications and inconvenience of haemodialysis and because it is less expensive, it offers the benefit of renal replacement therapy to a larger proportions of patients.

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