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Original Article

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Graft Survival in Preemptive Renal Transplantation in Children

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Abstract

Objective: Preemptive kidney transplantation (PKT) is an effective treatment modality that avoids the complications related to dialysis. However, the effect of PKT on graft survival remains controversial. This study aimed to compare graft survival in pediatric recipients of PKT with that of non-PKT recipients.

Materials and Methods: The medical records of pediatric kidney transplant recipients between 2005 and 2017 were retrospectively reviewed. We compared glomerular filtration rate, graft, and patient survival rates receiving PKT versus non-PKT.

Results: A total of 230 pediatric recipients were included in the study. The majority of recipients were boys (60.4%) who received a living donor kidney (70.8%). In the study group, 46.1% of the patients underwent PKT; 27.8% were on peritoneal dialysis and 26.1% on hemodialysis in the pre-transplant period. The rates of antibody-mediated rejection and BK virus nephropathy were similar between recipients with PKT and non-PKT (p=1.000 and 0.643, respectively). The 3-year graft and patient survival rates were similar between patients with PKT and non-PKT (95.2% vs 93.5%; p=0.776 and 98.1% vs 97.5%; p=1.000, respectively). The dialysis duration, rejection within 6 months after transplantation, and antibody-mediated rejection were independent risk factors for graft failure [Odds ratio (OR) 1.013; 95% confidence interval (CI) 0.992-1.034; p=0.031, OR 0.068; 95% CI 0.105-0.326; p=0.025, and OR 6.029; 95% CI 2.018-7.106; p<0.001].

Conclusion: Evaluation of graft and patient survival shows that PKT is a safe and effective renal replacement treatment option.

Keywords: Children, graft survive, kidney transplantation, preemptive

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INTRODUCTION

Preemptive kidney transplantation (PKT) is defined as kidney transplantation, which is performed before maintenance dialysis. Although dialysis is crucial for renal replacement therapy in many patients, the morbidity and mortality of patients on dialysis are significantly worse than in kidney transplant recipients (1, 2). Complications such as anemia, growth retardation, bone mineral disease, and impaired cognitive function are more common in children on dialysis. Theoretical advantages of PKT include avoiding the inconvenience of frequent hemodialysis sessions or frequent exchanges of peritoneal fluid, preventing significant morbidities associated with multiple access procedures, averting risks related to repeated blood transfusions, and the complications of prolonged uremia (3-6). As a result of these advantages, PKT reduces the overall cost of care and increases the number of working days of the patient (7).

Although PKT has been shown to be an ideal choice for renal replacement therapy, PKT rates have not reached the desired levels. The rate of choosing PKT as the initial renal replacement therapy has been reported to be between 13% and 24% in different studies (8, 9). Although the number of PKT procedures have gradually increased over the years after PKT was accepted as a safe renal replacement therapy, there is still a controversy over whether PKT has a positive effect on graft and patient

survival. Various studies that have addressed this issue have shown that graft and patient survival are better with PKT than with non-PKT (10, 11). However, a number of studies have reported that there was no difference between PKT and non-PKT (kidney transplantation after dialysis therapy) in terms of graft and patient survival (6, 7).

In this study, we aimed to determine the prevalence of pediatric PKT in our center and to compare graft survival in pediatric recipients of PKT with that of non-PKT recipients.

MATERIALS AND METHODS

Study Design and Patients

The data of pediatric patients who underwent renal transplantation between 2005 and 2017 were retrospectively evaluated. Patients with a minimum of 2 years of follow-up were included in the study. Patients who had a second kidney transplantation and without regular follow-up were excluded from the study. Baseline characteristics collected at PKT included: sex, age, primary kidney disease, dialysis method (peritoneal dialysis or hemodialysis), dialysis duration, and donor type.

Definition

PKT is defined as kidney transplantation before the initiation of chronic maintenance dialysis. The presence of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK polyoma virus (BKV) was checked for using monthly nucleic acid testing (NAT) for the first 3-6 months after transplantation and then every 3 months until the end of the first post-transplant year. The diagnosis of BKV nephritis was based on renal biopsy findings of patients whose BKV plasma NAT was greater than 10,000 copies/mL. Antibody-mediated rejection (AMR) was confirmed from biopsy findings and presence of donor specific antibodies. Estimated glomerular filtration rates (eGFR) at first year post-transplant and at last follow-up were calculated separately using the Schwartz formula. Patients who needed renal replacement therapy in the post-transplant period were declared as graft failure cases. Graft failure and mortality time after transplantation were recorded separately.

Immunosuppressive Protocol

Methylprednisolone was commenced as induction treatment on the day of the operation at a dose of 500 mg/m^2, which was decreased to 80 mg/m^2 on the second day after transplantation, and then gradually decreased until the maintenance dose of 5 mg/m^2/day was reached at third-month post-transplantation. In addition, an induction treatment with anti-thymocyte globulin or basiliximab was administered for recipients with human leukocyte antigen (HLA) mismatch >3. Cyclosporine A (CsA) or tacrolimus were used as calcineurin inhibitors. CsA was given orally twice a day at an initial dose of 5 mg/kg/day. Standard-release formulations of tacrolimus were started at a dose of 0.15 mg/kg twice daily on the day before the operation. In addition to calcineurin inhibitors, an antiproliferative agent (mycophenolate mofetil (1,200 mg/m^2/day), mycophenolic acid (860 mg/m^2/day), and prednisone (5 mg/day) were used as maintenance immunosuppressive treatments. Targeted plasma tacrolimus concentrations were as follows: 10-12 ng/mL for the first 6 months, 8-10 ng/mL for the next 6 months, and 4-8 ng/mL after the first year. The CsA target was 75-125 ng/mL until the end of month 2, and 50-100 ng/mL thereafter.

Statistical Analysis

Descriptive statistics were presented as frequency, percentage, mean, standard deviation, median, minimum, and maximum values. Shapiro-Wilks test, histogram, and Q-Q graphics were used for the normality test. The Pearson chi-squared test was used in the analysis of the relationships between categorical variables. Independent samples t-test was used for the comparison of normally distributed variables, and the Mann-Whitney U-test was used for the remaining comparisons. The Kruskal-Wallis test was used for the non-parametric comparison of the 3 disease groups, whereas the Mann-Whitney U-test was used as a post hoc test in significant cases. The Bonferonni correction was made for p values. Odds ratios (OR) and 95% confidence intervals (CI) were used in multiple logistic regression analysis for the assessment of risk factors. Multiple logistic regression analysis was also used for defining risk factors for graft failure. Statistical analyses were performed by using the IBM Statistical Package for the Social Sciences 21.0 packaged program (IBM SPSS Inc.; Armonk, NY, USA). P values <0.05 were accepted as statistically significant.

RESULTS

Characteristics of the Study Cohort at Transplantation

A total of 230 pediatric kidney transplant recipients were included in the study. The majority of recipients were boys (60.4%). The most common underlying diagnosis was congenital anomaly of the kidney and urinary tract (CAKUT) (42.1%). The mean age at the time of study was 15.33±5.41 years, mean age at transplantation was 11.03±4.83 years, and median follow-up period was 4.26 years (range 1.90-13.24 years). In the study group, 47.4% (n=109) of the patients were older than 12 years. A total of 163 patients (70.8%) received living donor kidneys. PKT was performed in 46.1% (n=106) of patients, 27.8% (n:64) were on peritoneal dialysis, and 26.1% (n:60) on hemodialysis treatment in the pre-transplant period. The median duration

Main Points

- The percentage of preemptive transplants among kidney transplants has been increasing over the years.
- Graft and patient survival rates were similar in preemptive and non-preemptive kidney transplantation.
- Graft survive was not different in living donor transplant and cadaveric donor transplant.
- Prolonged dialysis duration was found to be associated with graft failure.

of dialysis was 19.50 months (range 3-96 months) in the study population, and it was similar between the peritoneal dialysis and hemodialysis patients (31.34±2.95 vs 20.86±2.61; p=0.081).

Comparison of PKT versus Non-PKT

The mean age at the time of study, the mean age at transplantation, age group at transplantation, and the median follow-up period were similar between PKT and non-PKT recipients (p values of 0.570, 0.230, 0.304, and 0.814, respectively) (Table 1). The cadaveric donor ratio was higher in non-PKT recipients (36.2% vs 20.7%, p=0.002). The mean HLA mismatch count and the ratio of patient with HLA match ≥3 were similar between the 2 groups (3.08±1.17 vs 3.28±1.04; p=0.146 and 75.4% vs 68.5%; p=0.381, respectively). The use of tacrolimus compared with cyclosporine was found to be 83.0% in the PKT and 86.2% in the non-PKT (p=0.710) groups. The frequency of receiving induction therapies was similar between the 2 groups (p=0.153). The frequency of CMV infection, EBV infection, BKV nephropathy, and AMR were similar between PKT and non-PKT recipients (p values of 0.286, 0.115, 0.643, and 1.000, respectively).

Baseline Characteristics of Pediatric Kidney Transplant Recipients by Donor Type and PKT versus Non-PKT

PKT rates were 52.7% with living donor transplant and 29.8% with cadaveric donor transplant (p=0.001). Cadaveric renal transplantation and living donor kidney transplantation were evaluated separately; the median follow-up period, HLA mismatch count, frequency of opportunistic infection, and presence of AMR were similar between the PKT and non-PKT groups (Table 2).

Comparison of Graft Functions

The mean eGFR of PKT recipients at the first year of transplantation was lower than that of non-PKT recipients (73.82±5.50 vs 81.31±7.89 mL/min/1.73m^2; p=0.050); however, this difference was not present in the second year and thereafter (Table 1). The eGFRs of the recipients who received kidneys from cadaveric donors and living donors were evaluated separately; there was no difference in the eGFRs at 1 year, 3 years, and 5 years of transplantation between the PKT and non-PKT recipients (Table 2).

The mean eGFRs at 1 year, 3 years, and 5 years of transplantation were similar between adolescent recipients and recipients younger than 12 years of age (p values of 0.758, 0.179, and 0.368; respectively). Biopsy-proven AMR frequency was not more frequent in adolescent recipients (21.1% vs %16.5, p=0.236). In adolescent recipients, the 3-year eGFRs of the PKT recipients were worse than those of the non-PKT recipients (83.94±5.71 vs 97.67±7.51 mL/min/1.73m^2; p=0.012). However, this difference was not observed at fifth year of transplantation (75.32±6.76 vs 91.25±7.74 mL/min/1.73m^2; p=0.132).

Graft and Patient Survival

In all study cohorts, the 1-year and 3-year graft survival rates were 97.4% and 94.3%; and the 1-year and 3-year patient survival rates were 98.7% and 97.8%, respectively. The 1-year and 3-year graft survival rates were similar between the PKT and non-PKT recipients (99.0% vs 95.9%; p=0.221 and 95.2% vs 93.5%; p=0.776). In addition, patient survival rates were similar between the 2 groups (Table 1). Furthermore, graft survival and

Table 1. Patients characteristics at the time of transplantation in each group

	PKT (n=106)	Non-PKT (n=124)	p
Mean age (years)	15.03±5.45	15.59±5.38	0.570
Sex (male), %	69 (65.1)	70 (56.4)	0.278
Mean age of transplantation (years)	10.70±5.05	11.30±4.64	0.230
Age group at transplantation, years (%)			
≤5	26 (24.6)	18 (14.5)	0.304
5-12	30 (28.3)	47 (37.9)	
≥12	50 (47.2)	59 (47.6)	
Median follow-up period (years)	4.20	4.62	0.814
Cadaveric donor ratio (%)	22 (20.7)	45 (36.2)	0.002
Mean HLA mismatch	3.08±1.17	3.28±1.04	0.146
HLA match ≥3 (%)	80 (75.4)	85 (68.5)	0.381
Immunosuppression (%)			
Calcineurin inhibitors			
Tacrolimus	88 (83.0)	107 (86.2)	0.710
Induction therapy			
Only prednisolone	73 (68.8)	69 (55.6)	0.153
Antithymocyte globulin*	29 (27.3)	50 (40.3)	
Basiliximab**		4 (3.7)	5 (4.0)
CMV infection (%)	9 (8.4)	11 (8.8)	0.286
EBV infection (%)	5 (4.7)	4 (3.2)	0.115
BK virus nephropathy (%)	8 (7.5)	12 (9.6)	0.643
Rate of AMR (%)	20 (18.8)	23 (18.5)	1.000
Graft survival rate (%)			
1-year	99.0	95.9	0.221
3-year	95.2	93.5	0.776
Patient survival rate (%)			
1-year	100	97.5	0.251
3-year	98.1	97.5	1.000
eGFR (mL/m^2/min)			
1 year	73.82±5.50	81.31±7.89	0.050
3 years	64.41±6.82	71.37±11.44	0.066
5 years	57.20±4.52	66.37±11.85	0.321

*prednisolone used with antithymocyte globulin
** prednisolone used with basiliximab
PKT: preemptive kidney transplantation; CMV: cytomegalovirus; EBV: Epstein-Barr virus; AMR: antibody-mediated rejection

Table 2. Baseline characteristics of pediatric kidney transplant recipients by donor type and PKT versus non-PKT

	Cadaveric donor (n=67)			Living donor (n=163)		
	PKT (n=20)	Non-PKT (n=47)	p	PKT (n=86)	Non-PKT (n=77)	p
Mean age (years)	12.61±6.07	14.42±5.78	0.310	15.59±5.18	13.61±5.02	0.375
Sex (male) (%)	11 (55.0)	22 (46.8)	0.600	58 (67.4)	48 (62.3)	0.624
Mean age of transplantation (years)	9.20±5.07	10.81±5.13	0.232	11.05±5.02	11.61±4.32	0.456
Age group at transplantationyears (%)						
≤5	7 (35.0)	10 (21.3)	0.157	19 (22.1)	8 (10.4)	0.463
5-12	7 (35.0)	15 (32.0)		23 (26.7)	32 (41.6)	
≥12	6 (30.0)	22 (46.7)		44 (51.2)	37 (48.0)	
Median follow-up period (years)	4.10	3.40	0.288	4.30	4.25	0.882
Mean HLA mismatch	1.95±0.88	2.11±0.98	0.579	3.14±1.11	3.09±0.90	0.762
HLA match ≥3 (%)	6 (30.0)	17 (36.1)	0.571	75 (87.2)	67 (87.0)	0.968
CMV infection (%)	2 (10.0)	5 (10.6)	0.481	7 (8.1)	6 (7.7)	1.000
EBV infection (%)	1 (5.0)	2 (4.2)	0.147	4 (4.6)	2 (2.6)	0.685
BK virus nephropathy (%)	1 (5.0)	5 (10.6)	0.660	7 (8.1)	7 (9.0)	1.000
Rate of AMR (%)	1 (5.0)	9 (19.1)	0.260	19 (22.0)	14 (18.1)	0.564
Graft survival rate (%)						
1-year	95.0	91.4	0.528	100	98.7	0.472
3-year	95.0	89.3	0.415	95.3	96.1	0.561
Patient survival rate (%)						
1-year	100	95.7	0.489	100	98.7	0.472
3-year	100	95.7	0.489	97.6	98.7	0.542
eGFR(mL/m^2/min)						
1-year	88.96±2.77	94.88±4.22	0.351	117.62±10.11	104.07±10.74	0.165
3-year	80.44±2.95	84.36±4.89	0.149	94.07±11.61	96.90±10.85	0.890
5-year	72.26±3.29	77.92±4.71	0.364	76.23±5.69	77.96±5.64	0.956

PKT: preemptive kidney transplantation; CMV: cytomegalovirus; EBV: Epstein-Barr virus; AMR: antibody-mediated rejection

patient survival rates in PKT and non-PKT recipients were similar when evaluated separately in the cadaveric and living donor groups (Table 2).

Risk factors for graft failure evaluated using logistic regression analysis are shown in Tables 3 and 4. Dialysis duration (OR 1.021; 95% CI 1.006-1.038; p=0.011), donor sex (male) (OR 0.418; 95% CI 0.117-0.989; p=0.046), rejection within 6 months of transplantation (OR 0.047; 95% CI 0.016-0.134; p<0.001), and AMR (OR 21.452; 95% CI 7.458-61.705; p<0.001) were associated with the development of graft failure. However, PKT, cadaveric donor kidney, donor age. and HLA mismatches >3 were not found to be risk factors for graft failure. The 4 risk factors found significant in the univariate analysis were re-evaluated with multivariate analysis; dialysis duration, rejection within 6 months of transplantation, and AMR were independent risk factors for graft failure (OR 1.013; 95% CI 0.992-1.034; p=0.031, OR 0.068; 95% CI 0.105-0.326; p=0.025, and OR 6.029; 95% CI 2.018-7.106; p<0.001, respectively).

DISCUSSION

This study found that graft and patient survival rates were similar in recipients of preemptive and non-preemptive pediatric renal transplants. In the study cohort, at the 3-year follow-up post- transplant, 94.3% of the recipients had a functional graft kidney, and 97.8% of the recipients were alive. In addition, eGFR

Table 3. Evaluation of risk factors for graft failure in pediatric recipients by univariate logistic regression analysis

	OR	95% CI	p
PKT	1.815	0.744-4.427	0.190
Dialysis duration	1.021	1.006-1.038	0.011
Cadaveric donor	1.531	0.635-3.693	0.343
Donor age	1.030	0.949-1.119	0.476
Donor sex (male)	0.418	0.117-0.989	0.046
Rejection within 6 months after transplantation	0.047	0.016-0.134	<0.001
HLA mismatches >3	0.523	0.219-1.245	0.143
Acute cellular rejection	0.980	0.847-1.218	0.069
AMR	21.452	7.458-61.705	<0.001

PKT: preemptive kidney transplantation; OR: odds ratio; CI: confidence interval; AMR: antibody-mediated rejection

Table 4. Evaluation of risk factors for graft failure in pediatric recipients by multivariate logistic regression analysis

	OR	95% CI	p
Dialysis duration	1.013	0.992-1.034	0.031
Donor sex (male)	0.506	0.178-1.439	0.201
Rejection within 6 months after transplantation	0.068	0.105-0.326	0.025
AMR	6.029	2.018-7.106	<0.001

OR: odds ratio; CI: confidence interval; AMR: antibody-mediated rejection

distributions of the 2 groups were found to be similar during the study period. In the literature, several studies have documented better graft survival with PKT (9, 12). Amaral et al. (13) published a study examining a group of 7,527 pediatric renal transplant recipients, 1,668 of whom had PKT. They reported that the risk of graft failure was 52% higher in patients undergoing dialysis for more than 1 year compared to preemptive patients. In contrast, in a study in which 843 pediatric dialysis and transplant patients were investigated, it was found that PKT was not a factor affecting patient survival (14). In an article in which 324 patients were examined for postoperative complications, no differences between PKT and non-PKT recipients were found during 1 year of post-transplant follow-up (15).

The main factors that contributed to graft survival in the majority of studies were reportedly donor source and longer duration of dialysis when on the transplant waitlist (16). Moreover, in our study, we found that graft survival was similar in cadaveric and living donor kidney transplants in both PKT and non-PKT recipients. In a study by Cransberg et al. (17), PKT was shown to provide a positive effect on graft survival in cadaveric donor transplantation but not in living donor transplantation. However, PKT was not effective in patient and graft survival in patients with cadaveric donor kidney according to results from the French transplant network (18). Finally, in a study comprising 3,606 pediatric kidney transplantations, PKT was shown to reduce the risk of graft failure in living donor transplantation (19).

In this study, the dialysis duration was 19.50 months, and this was found to significantly increase the risk of graft failure (OR 1.013; 95% CI 0.992-1.034; p=0.031). According to a study by Kim et al. (20), the survival and death-censored graft survival rate was found to be worse in patients with dialysis longer than 19 months. In another study evaluating pediatric kidney transplant recipients, the rate of graft loss increased by 52% in those who received dialysis therapy longer than 12 months compared to preemptive recipients (13). It is believed that PKT does not benefit when it is done early; however, kidney transplantation provides better patient and graft survival when GFR is reduced, but before the negative effects of dialysis occur (21, 22).

In a study evaluating 22,345 adult recipients, the median pre-transplant dialysis duration was 2.3 years in patients who had non-PKT (16). In the Eurotransplant study, the dialysis exposure time was 14.7 months in living donor kidney transplant recipients and 18.7 months in cadaveric kidney transplant recipients. Of the 1,113 patients followed in this study, 80% received kidneys from cadaveric donors (17). In our study, the duration of dialysis was found to be longer than prior studies investigating pediatric transplant recipients. In our opinion, the main reason for this longer period is the low rate of cadaveric donations in our country.

In this study, we determined that both rejection within 6 months after transplantation and AMR were independent risk factors for graft failure [OR 0.068; 95% CI 0.105-0.326; p=0.025 and OR 6.029; 95% CI 2.018-7.106; p<0.001, respectively]. The negative effect of AMR on graft survival was evident in many studies (23, 24). However, the frequency of AMR was similar in PKT and non-PKT recipients.

In our study, no relationship was observed between EBV, CMV, and BKV infections and PKT. Okumi et al. (25) found that PKT was not superior to non-PKT in reducing the risk of biopsy-proven rejection. The same study found the risk of CMV infection similar in both groups.

In our study, we found that the 3-year graft function of the adolescent age group was worse than that of other age groups; however, this difference was lost in the following years. In the literature, adolescent recipients have shorter graft survival than younger recipients (26). Rejection episodes owing to medication nonadherence are more common in the adolescent age group (27). However, in our study, we did not find an increase in the prevalence of biopsy-proven AMR in the adolescent age group.

In this study, the percentage of PKT procedures was 46% in all pediatric kidney transplants, 53% in living donor transplants, and 30% in cadaveric donor transplants. The frequency of PKT in our study was found to be higher than in many other studies in the literature (16-18). In a large-scale study evaluating pediatric renal transplantation in 2010 and 2012, the frequency of PKT ranged from 22% to 25% (3, 28). In the majority of studies evaluating adult kidney transplantation, the rate of PKT was lower than that of pediatric patients. In many countries, organ donation systems aim to protect children, as is the case in our country. In addition, the kidneys of pediatric donors are presented primarily to pediatric patients with end-stage renal disease (ESRD) in accordance with the current organ and tissue distribution directive in our country.

Our study had some limitations, related to the retrospective nature of the study, including the inability to evaluate potential confounders. The patients' adherence to medication and other conditions affecting graft survival (such as urinary tract infections and long-term surgical complications) were also not assessed during the study. Our study also had a smaller sample size than many other similar studies presented in the literature.

Despite the limitations, the high frequency of PKT compared with non-PKT (almost 1:1 ratio) is an important feature of this study. From this viewpoint, it is apparent that our study had a better group distribution which could result in better statistical evaluation. This study compared pediatric kidney transplant recipients with both graft and patient survival and annual eGFR monitoring. In addition, opportunistic infections (such as EBV, CMV, and BKV), which may lead to graft loss were included in the study along with rejection.

CONCLUSION

Our findings showed that graft and patient survival rates were similar in both cadaveric and living donor kidney transplant recipients who underwent PKT. To avoid any adverse effects related to dialysis, all patients with ESRD should be informed about the option of PKT, and appropriate patients should undergo kidney transplantation without delay.

Ethics Committee Approval: Ethics committee approval was not received for this study.

Informed Consent: Informed consent was not obtained due to the nature of this study.

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