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A single-center nine-year experience in pediatric kidney transplantation

Çocukluk çağı böbrek naklinde 9 yıllık tek merkez deneyimi

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SUMMARY

Objective: The success rates of renal transplantation in pediatric age groups increased rapidly with the improvement of surgical technique, development of immunosuppressive drugs and the establishment of follow-up protocols specific to the pediatric age group and achieved the success rates of adult transplantation. In this study, we retrospectively analyzed the results of pediatric renal transplants performed in our center in 9 years.

Method: Between January 2010 and December 2018, 41 pediatric renal transplants were performed in our center. In our study, demographic data of donors and recipients, immunosuppressive treatment protocols applied to the recipients, post-transplant complications and renal functions of these donors were evaluated.

Results: Mean age of the recipients was 13.44 ± 3.72 and 48.8% of the recipients were female. The mean follow-up period was 46.90 ± 30.04 months. During the follow-up period, no complications due to surgery developed. One patient (2.4%) had urologic complications requiring endoscopic intervention. One patient (2.4%) had sepsis-related mortality, one patient (2.4%) had recurrence of primary disease, and three patients (7.2%) had graft loss due to medical noncompliance. The mean age was 43.15 ± 9.28 years and 53.7% of the donors were female . During the follow-up, wound-related complications were observed in two patients (4.8%). There was no change in renal function detected.

Conclusions: The results of our study show that pediatric renal transplantation was performed safely and successfully in our center when compared with the literature data published from the studies conducted in centers with high number of patients and systematic reviews.

Keywords: Pediatric transplantation, kidney transplantation, kidney, renal transplantation, transplantation



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ÖZET

Amaç: Çocukluk çağı böbrek nakli başarı oranları, cerrahi teknik ve immunsupresif ilaçlardaki gelişmeler ile çocukluk çağına özgü takip protokollerinin uygulanmaya başlanmasına bağlı olarak hızlıca arttı ve erişkin nakillerinin başarı oranlarına ulaştı. Bu çalışmada, merkezimizde 9 yıllık süreçte yapılan çocukluk çağı böbrek nakillerinin sonuçlarını retrospektif olarak analiz ettik.

Yöntem: Ocak 2010 ve Aralık 2018 arasında, merkezimizde çocukluk çağındaki 41 hastaya böbrek nakli uygulandı. Çalışmamızda, verici ve alıcıların demografik verileri, alıcılara uygulanan immunsupresif protokoller, vericilerin nakil sonrası komplikasyonları ve böbrek fonksiyonları değerlendirildi.

Bulgular: Alıcıların ortalama yaşı 13.44 \pm 3.72 idi ve alıcıların %48.8'i kadındı. Ortalama takip süresi 46.90 \pm 30.04 aydı. Takip süresi boyunca cerrahiye bağlı bir komplikasyon gelişmedi. Bir hastada (%2.4) endoskopik girişim gerektiren ürolojik komplikasyon meydana geldi. Bir hastada (2.4%) sepsise bağlı ölüm, bir hastada (2.4%) primer hastalık nüksü, 3 hastada ise (%7.2) medikal tedaviye uyumsuzluk nedeniyle greft kaybı görüldü. Vericilerin ortalama yaşı 43.15 \pm 9.28 yıldı ve %53.7'si kadındı. Takip süresi boyunca, 2 hastada yara yerine bağlı komplikasyon gözlendi (%4.8). Böbrek fonksiyonlarında ise değişiklik saptanmadı.

Sonuç: Çalışmamızın sonuçları, literatürdeki yüksek hasta sayısına sahip merkezlerin ve sistematik derlemelerin verileriyle kıyaslandığında, merkezimizde çocukluk çağı böbrek nakillerinin güvenli ve başarılı bir şekilde uygulandığını göstermiştir.

Anahtar sözcükler: Pediatrik transplantasyon, böbrek nakli, böbrek, renal transplantasyon, transplantasyon.

INTRODUCTION

The most common causes end-stage renal disease in the pediatric age group are congenital, cystic and hereditary disorders comprising the 38% of the total cases. In adolescence, primary and secondary glomerular diseases are identified as the most common causes¹. Kidney transplantation is the preferred treatment choice for end-stage renal disease in the pediatric age group. It provides a longer lifespan, skeletal system development, increased health-related quality of life, and neuropsychological development, when compared to dialysis^{1,2}. Kidney transplantation has rapidly gained acceptance and become widespread in adult patients as a treatment modality. It has also been used in the pediatric age group despite in the past, high morbidity and mortality rates due to the difficulties in surgical techniques and long-term immunosuppressive drug use. However, today the procedure has been developed such that the success rates for pediatric transplantations have more successful outcomes than adult transplantation rates³. There are several reasons for this increase in including improved clinical success, and immunological evaluation of patients, improvements in surgical management and supportive therapies. innovations in immunosuppressive therapies, appropriate cardiovascular support, and infection control specific to the pediatric age group^{4,5}. One and fiveyear graft survival rates after renal transplantation, in pediatric patients, have been reported to be 96% and 81%, respectively⁶. The most important improvement in graft and patient survival rates was year for the first after the transplantation⁷. However, the potential for complications after renal transplantation is higher in the pediatric patient group than in adult patients^{2,8,9}.

Donor and recipient age, gender, body mass index, warm ischemia time, donor status (living vs. cadaver), the surgeon's level of experience, and compliance to the follow-up and medication are the most important factors that affect the postoperative morbidity, and graft function. The donor outcomes have improved over time with the implementation of minimal invasive surgical techniques. In this study, we evaluated the results of pediatric renal transplants performed in our center.

MATERIAL AND METHODS

41 pediatric patients who underwent renal transplantation in our center between January 2010 and December 2018 and their donors, were evaluated retrospectively. Follow-up data until July 2019 included in the were evaluation. Demographic data such as age, sex and body mass index, clinical data such as etiologic causes of renal failure, duration of hospitalization, which side the kidney was procured (laterality), duration of operation that the donor and recipient underwent, number of arteries, ureteral stent placement, and immunosuppressive treatment protocols, complications and graft and patient survival were evaluated.

Antithymocyte globulin (ATG) (6-8 mg / kg, cumulative dose) or Basiliximab (20 mg, Postoperative Day 0 and Day 4) was administered to a substantial group of the recipients as an induction regimen. In one recipient weighing less than 10 kg half dose of Basiliximab therapy (10 mg.) was applied. The maintenance regimen was continued with standard triple therapy including calcineurin inhibitors, antimetabolites and steroids.

In this study, delayed graft function was defined as the condition of the need for dialysis for any reason in the first week following the transplantation and slow graft function was defined with a creatinine level >2.5 mg/dL at the 5^{th} day following transplantation.

Surgical technique: Except one patient, renal performed transplantation was to the retroperitoneal area of the recipient with open approach as a standard procedure. As one patient was <2 years of age and <10 kg, the graft was placed into the abdomen after removal of the native kidneys. Depending on suitability, renal artery anastomosis to the external or common iliac artery, and renal vein anastomosis to the external and common iliac vein were performed, except one patient who had arterial anastomosis to aorta and vein anastomosis to vena cava. The Lich Gregoir technique was used in ureter anastomosis. Ureteral stenting was not performed as a standard procedure, however, was performed on patients who were thought to be at risk of surgical complications or have immunological risk. The donors underwent handassisted retroperitoneoscopic donor nephrectomy as a standard procedure. All patients received a single dose of Ampicillin-Sulbactam (50 mg / kg) prophylaxis prior to their surgery.

Statistical analysis: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used in the evaluation of data. Normal distribution of the quantitative data was analyzed by using the Kolmogorov-Smirnov test, Shapiro-Wilk test and graphical evaluations. The Mann-Whitney U test was used for comparison of the two groups when the data did not follow a normal distribution. The Wilcoxon signed-ranks test was used for intragroup comparisons of non-normally distributed parameters. A p value lower than 0.05 was accepted as statistically significant.

RESULTS

Recipient findings: Between January 2010 and December 2018, 41 pediatric patients in our center underwent renal transplantation. 20 patients had hemodialysis and 8 had peritoneal dialysis as renal replacement therapy prior to the transplantation. 13 patients were preemptive. The most common causes of end-stage renal disease were primary glomerular disease and vesicoureteral reflux (17%). In 29% of cases, primary cause could not be determined (Table 1). The mean age of the patients was 13.44 ± 3.72 years and 51.2% (n = 21) of them were male. The age groups of the recipients are shown indicated Table 2. The mean body mass index of the patients was 19.22 ± 5.90 kg/m². All transplants were from living donors. The mean duration of hospitalization of the recipients was 7.54 ± 2.71 days and the mean follow-up period 46.90 ± 30.04 months. Demographic was characteristics of the recipients, their early and late clinical findings after transplantation and renal function during follow-up are indicated in Table 3.

Table 1: Recipients' etiology of end-stage renal disease

7 (17%)
3 (7.3%)
3 (7.3%)
2 (4.8%)
7 (17%)
3 (7.3%)
4 (9.7%)
12 (29.2%)

Table 2: Distribution of the recipients according to age groups

Age (years)	No of patients
0-2	1 (2.4%)
3-6	1 (2.4%)
7-12	12 (29.2%)
13-18	27 (65.8%)

Table 3: Demographic characteristics and posttransplant outcomes of the recipients.

Recipient characteristics (n=41)		n (%)
Age (year)	Min - Max	2 - 18
	$Mean \pm Sd$	13.44 ± 3.72
Sex	Female	20 (48.8)
	Male	21 (51.2)
BMI (kg/m ²)	Min - Max	13 - 47.2
	$Mean \pm Sd$	19.22 ± 5.90
Hospitalization period (day)	Min - Max	5 - 16
	$Mean \pm Sd$	7.54 ± 2.71
Follow-up period (month)	Min - Max	5 - 112
	$Mean \pm Sd$	46.90 ± 30.04
Pre-transplant renal replacement	Preemptive	13 (31.7)
therapy	Peritoneal dialysis	8 (19.6)
	Hemodialysis	20 (48.7)
Delayed graft function	No	41 (100)
	Yes	0 (0)
Slow graft function	No	40 (97.6)
	Yes	1 (2.4)
Ureteral stent implementation	No	26 (63.4)
	Yes	15 (36.6)
Urologic complication	No	41 (100)
	Yes	1 (2.4)
Recipients' status at the end of	Functioning kidney	32 (78.0)
follow-up period	Hemodialysis	4 (9.8)
	Excitus	1 (2.4)
	Out of follow up	4 (9.8)
5th day serum creatinine (mg/dl.)	Min -Max (Median)	0.2 – 2.9 (0.7)
	$Mean \pm Sd$	0.83 ± 0.48
1st month serum creatinine	Min -Max (Median)	0.3 - 2.8 (1)
(mg/dl.)	$Mean \pm Sd$	0.98 ± 0.44
6th month serum creatinine	Min -Max (Median)	0.5 - 4.1 (1)
(mg/dl.)	$Mean \pm Sd$	1.15 ± 0.64
1st year serum creatinine (mg/dl.)	Min -Max (Median)	0.6 - 2.3 (1)
	Mean ±Sd	0.99 ± 0.33
Last control creatinine (mg/dl.)	Min-Max (Median)	0,5 - 10,3 (1,1)
	Mean±Sd	1.99 ± 2.40

During the follow-up period, none of the patients had delayed graft function and one patient (2.4%)had grade 2-3 hydronephrosis at the transplanted kidney due to ureteral reflux requiring endoscopic intervention one-year post-transplantation. Four patients from outside the province who underwent transplantation in our center, continued their follow-up in other centers. One patient with primary disease recurrence (Focal segmental glomerulosclerosis), and three patients with immunosuppressive medication noncompliance (in the adolescent group) had graft loss. The mean duration of graft loss after transplantation was 2.4 years in these patients. During the follow-up period, one patient died due to sepsis, secondary to an influenza infection at the fifth month posttransplantation. One-year graft, and patient survival rates were 95.1%, and 97.6% (40/41), and three-year graft, and patient survival rates were 92.6%, and 97.6%, respectively.

When the renal functions of the recipient group were evaluated, there was a statistically significant increase in the creatinine levels on the 5th day after transplantation, compared to the levels at the last control (p = 0.001; p < 0.01). We then examined whether the transplanted graft was the right or left kidney, or whether there was a ureteral stent placement into the recipient, or whether the transplanted graft having one or more arteries had an impact on early and late graft function, and the length of hospital stay of the recipient. In the evaluation, there were no significant effects of that laterality of grafted kidney on the renal function on the 5th day and at the last control, and on the length of hospital stay after transplantation (p = 0.75, p = 0.73). However, there was a significant increase in the 5th day and the last control creatinine levels in both groups (Table 4). When the results of the ureteral stent placement into the recipient were evaluated, no significant differences were found between the early and late term results, as well as the number of hospitalization days (p = 0.37, p = 0.79) (Table 5). Evaluation of the effect of the number of arteries in the transplanted graft (one or more arteries) on renal function, revealed a significantly higher increase in the renal function of the grafts with a single artery, between the 5th day and the last control date. Whereas, the increase in renal functions of grafts with multiple arteries was not statistically significant (Table 6). There was no difference between the two groups in terms of the length of hospital stay.

Donor findings: The mean age of the patients was 43.15 ± 9.28 years, and 53.7% (n = 22) were female and 46.3% (n = 19) were male. The mean body mass index of the donors was 28.68 ± 4.32 kg / m². 29 patients (70.7%) underwent left and 12 patients (29.3%) underwent right nephrectomy. 12.2% of the donors had multiple renal arteries. The surgical dissection time of the donor was 90.73 ± 27.23 minutes and the mean cold ischemia time of the transplanted kidney was 81.24 ± 22.87 minutes. Since hand-assisted surgical technique was used, the mean warm ischemia time was less than two minutes in all cases. The mean serum creatinine levels on the first day post- transplantation were 0.99 ± 0.24 mg. / dL., mean follow-up time was 37.07 ± 27.29 months, and mean serum creatinine levels at the end of the follow-up period were 1.02 \pm 0.26 mg. / dL. (Table 7). After donor nephrectomy, one patient had wound infection (2.4%), one patient had incisional hernia (2.4%) and one patient had chronic pain on the wound area (2.4%). There was no significant increase in serum creatinine levels of the donors during the follow-up period (p = 0.26).

Table 4: Comparison of early and late graft function and duration of postoperative hospitalization with regards to kidney laterality

			Kidney latera	ality	
n=41	C		Right kidney (n=12)	Left kidney (n=29)	p
Recipients'	5th day	Min / Max			^a 0.166
creatinine		(Median)	0.4 / 2.9 (0.85)	0.2 / 1.7 (0.7)	
levels		$Mean \pm Sd$	1.02 ± 0.66	0.75 ± 0.37	
(mg/dl.)	Last	Min / Max			^a 0.677
	control	(Median)	0.5 / 7 (1.2)	0.5 / 10.3 (1.1)	
		$Mean \pm Sd$	2.06 ± 2.26	1.96 ± 2.49	
		^b p	0.028*	0.001**	
	Difference	Min / Max			^a 0.752
		(Median)	-0.7 / 6.1 (0.3)	-0.3 / 9.6 (0.4)	
		$Mean \pm Sd$	1.04 ± 1.94	1.20 ± 2.38	
Hospitalization		Min / Max			^a 0.736
period (day)		(Median)	5 / 13 (7)	5 / 16 (7)	
		$Mean \pm Sd$	7.75 ± 2.73	7.45 ± 2.75	

^aMann-Whitney U Test

^bWilcoxon Signed-Ranks Test *p<0.05 **p<0.01

Table 5: Comparison of early and late graft function and duration of postoperative hospitalization with regards to ureteral stent implementation

eral stent placement p
26) Yes (n=15)
a0.3
7 (0.7) 0.4 / 2.9 (0.8)
0.39 0.93 ± 0.60
a0.1
4 (1.1) 0.5 / 10.3 (1.3)
1.94 2.70 ± 2.96
* 0.001**
a0.3
.1 (0.35) -0.1/ 9.6 (0.3)
1.78 1.77 ± 2.83
a0.7
7) 5 / 13 (7)
2.86 7.40 ± 2.53

			No of graft artery		
n=41			Single artery (n=36)	Multiple arteries (n=5)	р
Recipients'	5th day	Min/ Max			^a 0.841
creatinine		(Median)	0.2 / 2.9 (0.7)	0.5 / 1.1 (0.7)	
levels		$Mean \pm Sd$	0.84 ± 0.50	0.78 ± 0.26	
(mg/dl.)	Last control	Min/ Max			^a 0.090
		(Median)	0.5 / 10.3 (1.2)	0.6 / 1.1 (1)	
		Mean ±Sd	2.14 ± 2.52	0.88 ± 0.22	
		^b p	0.001**	0.102	
	Difference	Min / Max			^a 0.040*
		(Median)	-0.7 / 9.6 (0.4)	0 / 0.3 (0.1)	
		$Mean \pm Sd$	1.30 ± 2.35	0.10 ± 0.12	
Hospitalization		Min / Max			^a 0.791
period (day)		(Median)	5 / 16 (7)	5 / 13 (7)	
		$Mean \pm Sd$	7.50 ± 2.71	7.80 ± 3.03	
Mann-Whitney U Test	^b Wilc	oxon Signed-Ranks Test	*p<0.05	**p<0.01	1

Table 6: Comparison of early and late graft function and duration of post-operative hospitalization with regards to number of graft artery

^aMann-Whitney U Test

Table 7: Donor characteristics and surgical data

	n (%)
Min -Max (Median)	22 - 71 (42)
$Mean \pm Sd$	43.15 ± 9.28
Female	22 (53.7)
Male	19 (46.3)
Min -Max (Median)	21.7 - 37.6 (28.1)
$Mean \pm Sd$	28.68 ± 4.32
Min -Max (Median)	0.7 - 1.6 (0.9)
$Mean \pm Sd$	0.99 ± 0.24
Min -Max (Median)	0.7 - 1.6 (0.9)
$Mean \pm Sd$	1.02 ± 0.26
Min -Max (Median)	1 - 94 (39)
$Mean \pm Sd$	37.07 ± 27.29
Right	12 (29.3)
Left	29 (70.7)
Min -Max (Median)	45 - 150 (90)
$Mean \pm Sd$	90.73 ± 27.23
Single artery	36 (87.8)
>1 arteries	5 (12.2)
Min -Max (Median)	40 - 132 (80)
$Mean \pm Sd$	81.24 ± 22.87
	Mean \pm SdFemaleMaleMin -Max (Median)Mean \pm SdMin -Max (Median)Mean \pm SdMin -Max (Median)Mean \pm SdMin -Max (Median)Mean \pm SdRightLeftMin -Max (Median)Mean \pm SdSingle artery>1 arteriesMin -Max (Median)

DISCUSSION

^aMann

In our series, the causes of end-stage renal failure, in accordance with the United States Renal Data System, were hereditary and cystic disorders in younger pediatric age group and glomerular

diseases in adolescents¹. Twenty-seven of the transplanted patients (65.8%) were older than 13 years. In the 2014 annual report data of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), cases between the ages of 13-

17 (39.2%) were the most common transplant $\operatorname{group}^{10}$. Refraining from transplant-related complications and evaluation of transplantation option only after dialysis-related complications and growth and developmental retardation begins may be the cause of delay in the pediatric age group. Despite the high mean age, 31.7% of our recipients were received a preemptive transplantation, consistent with US data with an average preemptive pediatric transplant rate of 30%¹¹. In addition, although it was indicated in NAPRTCS data that 50% of transplantations were from deceased donors, all transplants in our series were from living donors. We think that the reasons of preference of live donor transplants is higher graft and patient survival rates in live donor transplantation and delay and uncertainty in deceased donor programs.

The recipient age and source of the transplanted kidney are the two most important prognostic factors in renal transplantation in pediatric age groups¹². During the follow-ups between the period of 2006 and 2010, one- and five-year graft survival after living donor transplantation was 96.5% and 86.1%, respectively, and the best graft survival was detected as 89.1% in recipients under 11 years of age. The adolescent patient group has the worst five-year survival results in all age groups including the adults^{13,14}. NAPRTCS data, on the other hand, reported the one- and three-year survival results in live donor transplantations as 96.4% and 93.4%, respectively. In our series, oneand three-year graft survival was 95.1% and 92.6%, respectively, similar to the literature. In the first year of post-transplantation, graft loss occurred in one patient due to recurrence of primary disease. One recipient died of influenza virus-induced sepsis in the fifth month after transplantation. Transplant patients may have more severe and prolonged viral infections due to their immunosuppressed status. In this patient group, it is recommended to start inactivated vaccination 3-6 months after transplantation¹⁵. In our follow-up protocol, we also start inactivated vaccination after 6 months, but after the sepsis case at 5 months, we think that the timing of vaccination may be applied earlier than the standard protocol as patient-oriented and depending on their sociocultural assessment and hygiene conditions.

Nonadherence to immunsupressive medication is an another determinant that affects graft survival in pediatric kidney transplant recipients. Strivastata et al. showed that only 61% of the recipients regularly used immunosuppressive drugs in the 5-year period after transplantation¹⁶. In their study, Shemesh et al. reported that rate of noncompliance with medical recommendations could reach up to 75% in adolescent patients and that pediatric patients were critically vulnerable during their transition to adulthood¹⁷. In our study, three recipients in the adolescent age group (7.3%) lost grafts due to noncompliance with drug recommendations despite the strict follow-up protocol and intermittent education. Poor family dynamics and poor psychosocial dynamics of the child are shown as the two most important causes of non-compliance in this age group patient¹⁸.

After kidney transplantation, up to 40% of the patients are re-hospitalized due to various reasons19. Surgical complications can be encountered during or immediately after transplantation. Vascular thrombosis, the most important cause of graft loss in the early period, has been reported in 2-12% in various case series^{20, 21}. Lymphocele development is another common complication is at a rate of 1-25%, but 5% become symptomatic²². In our series, no patients had vascular thrombosis or lymphocele. Since the donor kidney could cause compartment syndrome in the recipient, kidney in a single case weighing less than 10 kg was placed into the peritoneum and bilateral native nephrectomy was performed to make room for the graft. The other cases weighed more than 15 kg, therefore, the transplant graft was placed extraperitoneally without any challenges. The incidence of urological complications after renal transplantation in pediatric age varies between 3% and 15%. Presence of bladder dysfunction, obstructive uropathy and vesicoureteral reflux (VUR) in the pre-transplant patient is associated with the incidence of posttransplant urological complications²³⁻²⁵. During the follow-up period, VUR was detected in a transplant kidney in one recipient and the patient was hospitalized several times for recurrent febrile urinary tract infections. Consistent with the literature, this patient also had pre-transplant VUR. The patient was then treated by endoscopic method. When the graft functions of the recipients included in the study were evaluated, a significant increase was found in the graft functions measured at the last controls during the follow-up when compared to the graft functions on the fifth day after post-transplantation. We think that the inclusion of creatinine measurement of recipients who have graft loss at the last control is the reason for the significant increase in data. Factors which may affect the graft function especially in the early period as the laterality of the donor kidney, number of arteries of the transplanted kidney, and ureteral stent placement did not have any significant effect on either graft function or duration of hospital stay. Contrary to expectations, increase in the creatinine levels was found to be higher during the follow-up period in grafts having single artery. We think that this is related to the fact that the grafts of the recipients requiring dialysis for different reasons after transplantation had a single artery.

When the donor findings were examined, no complications such as bleeding due to surgery, conversion to open surgery and intra-abdominal organ damage were detected. During three years of follow-up, incisional hernia developed in one donor and wound infection in another donor. The reason for this may be that the donors were operated by hand-assisted retroperitoneoscopic method, where patient safety is at the forefront and the risk of surgical complications is minimal due to the protection of intra-abdominal integrity, however, as with all hand-assisted surgery, wound complications are relatively common in this technique²⁶. On the other hand, there was no increase in creatinine levels of the donors during the follow-up period.

The retrospective nature of the study and the limited number of cases can be considered as limitation criteria. In conclusion, renal transplantation in pediatric age increases patient survival and reduces morbidity associated with end-stage renal failure. Despite the small number of cases in our series, renal transplantation is performed safely and successfully in our center when compared with the literature.

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