

# KIDNEY TRANSPLANTATION IN CHILDREN: RESULTS OF TEN YEARS EXPERIENCE IN IMAM REZA HOSPITAL

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## ABSTRACT

Advances in nephrology and pediatric urology have increased the number of children who survive renal disease and become candidates for renal transplantation. Ten years of experience in pediatric renal transplantation are reviewed to determine the rates of patient morbidity and graft survival.

Of the 450 renal transplantations performed in Imam Reza Hospital (1989-1999), fifty-one were done on children (6-18yrs.). Causes of renal failure included: reflux nephropathy, 8 cases; neurogenic bladder, 5 cases; posterior urethral valve, one case; prune belly syndrome, 1 case; small kidney due to chronic glomerulonephritis, 8 cases; the remaining failures were of unknown etiology.

All kidneys were harvested from living donors,<sup>30</sup> related and unrelated.<sup>20</sup> Immunosuppressive therapy was given with three drugs in all children: prednisolone, azathioprine, and cyclosporine, with the exception of 6 recipients of HLA-identical siblings who did not receive cyclosporine. The Kaplan-Meier curve was constructed to assess graft and patient survival and the Log rank test was used to assess the effect of kidney source and date of renal transplant.

Immediate diuresis occurred in all grafts. Surgical complications included two urinary fistulae and one clinical lymphocele which were all repaired surgically. There were eleven acute rejections. The most common causes of graft failure were chronic rejection and recurrence of primary renal diseases. The graft survival rates after 1, 2, 5 and 10 years were 95%, 84%, 76%, and 62% respectively.

By all measures, renal transplantation is still the treatment of choice for children with ESRD. Renal transplantation in children results in improvement in physical growth, mental development and rate of survival. Hypertension, chronic rejection, infection, obesity and medical noncompliance continue to be problematic.

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## INTRODUCTION

The incidence of renal failure in children has been put at approximately 11 per million for children from birth to nine-

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teen years, according to the US Renal Data System.<sup>26</sup> Renal failure in childhood leads to growth retardation, osteodystrophy and CNS morbidity.<sup>19,24</sup> Children have low tolerance to being "dependent" on the dialytic modality. Maintenance dialysis induces loss of self-esteem and emotional maladjustments.<sup>16</sup> Transplantation is, therefore, the treatment of choice for nearly all children with renal failure.<sup>1</sup>

The first pediatric renal transplantation in Imam Reza Hospital was performed in 1989 and the recipient continues to have normal renal function. Since that time, we have performed 50 additional renal transplantations in children. The purpose of this study is to present our experience with pediatric renal transplantation at our center.

### PATIENTS AND METHODS

From 1989 to 1999, 450 renal transplantations were performed. Among these, 51 were performed on 49 children (2 repeats), 6-17 years of age (mean age 12.9). There were 32 male and 19 female recipients. All kidneys were harvested from live donors. These included 24 related donors (12 mothers, 6 fathers, 3 brothers, 3 sisters) and 21 unrelated donors. At the time of transplantation, 42 were on hemodialysis and the remainder had never received maintenance dialysis.

Pre-transplantation assessments included medical and surgical history, physical examination, urinalysis, urine culture, liver function tests, serum electrolytes, ultrasonography of the native kidney, and voiding cystourethrography (VCUG). HLA tissue typing was done only between recipient and relative living donors but panel reactive antibody testing and pretransplant cross match between recipient serum and donor lymphocyte was performed for all patients.

The most common medical problems before transplantation were growth failure (70%), hypertension (75%), and osteodystrophy (30%). Pre-transplant bilateral nephroureterectomy due to vesicoureteral reflux grade V was performed in five children, and augmentation cystoplasty due to neurogenic contracted bladder with a segment of sigmoid in 1 patient and dilated ureter in 2 patients. A vertical lower pararectus incision with retroperitoneal placement of the graft in the pelvis was used in 49 transplants. In two children with weight less than 20 kilograms a transperitoneal vertical midline incision was used.

Immediately after donor nephrectomy, the kidneys were cooled and washed by intra-arterial infused cold heparinized lactated Ringer's solution for about five minutes. There were 2 donor kidneys with 2 renal arteries. We used the "pants" technique to join the vessels side by side and the end to end anastomosis to the internal iliac artery was performed. In two small children, the artery of the graft was sutured to the aorta and the vein to the inferior vena cava. In the other cases, the artery of the graft was anastomosed to the internal iliac artery (end to end), and the vein of the graft

was anastomosed to the external iliac vein of the recipient (end to side) with 6-0 or 5-0 nylon sutures.

During the vascular anastomosis we infused 0.5 mg/kg of Mannitol (20% solution), and 1-10 mg/kg furosemide. Normal saline (N/S) or 5% dextrose saline solution (D/S) was infused to maintain the systolic pressure above 120 mmHg just before releasing the clamp. In cases with immediate diuresis, we rapidly infused about 500 mL D/S or N/S immediately after releasing the vascular clamp.

Urinary tract reconstruction was performed by extravesical ureteroneocystostomy and insertion of a double J stent in 48 cases. In three children with small bladders, Ledbetter Politano ureteroneocystostomy was performed and a ureteral catheter (nelaton No. 8) was brought out from the bladder wall for temporary diversion. The urethral catheter and ureteral double J stent were removed 5 to 7 days and 6 weeks after renal transplantation respectively.

Immunosuppression therapy was given with three drugs in 45 children (prednisolone-azathioprine-cyclosporine) but for 6 recipients from HLA-identical siblings, allografts did not receive cyclosporine.

Average length of hospital stay was 19 days. Follow-up ranged from 1 to 10 years; 60% of the recipients were followed for 5 years or more, 30% for 2 to 5 years, and 10% for less than 2 years.

To assess graft and patients survival we constructed the Kaplan-Meier curve and the Log Rank test was used to compare survival rates between the subgroups-recipients of related donors, and of unrelated donors-with a finding of  $p=0.02$ , which is significant.

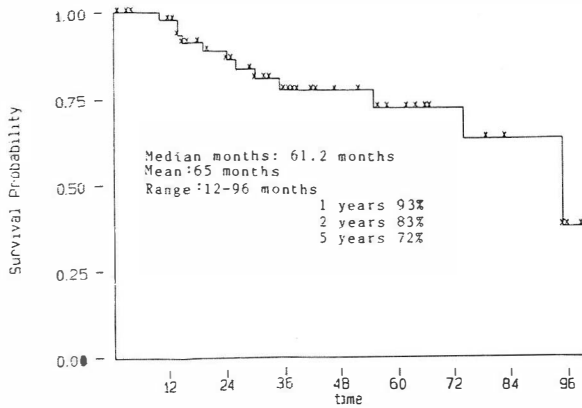
### RESULTS

Immediate diuresis occurred in all grafts. There were two cases of end ureteral necrosis and urinary leakage which were repaired accordingly. Clinical lymphocele occurred in one recipient one month after transplantation which was treated surgically. In one patient, three years after transplantation, the left native kidney was removed due to pyonephrosis.

Acute rejection occurred in 11 children but responded to pulse therapy. At the time of last follow-up, 16 of the recipients (32%) required treatment for hypertension. Obesity was present in 28% and short stature in 23%. Chronic rejection was observed in fourteen patients.

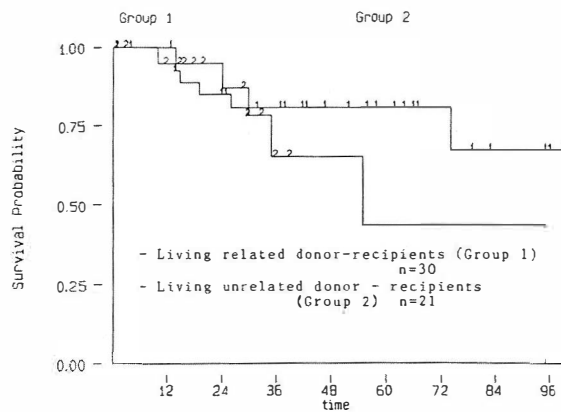
In three other children serum creatinine was about 2.8 mg/100 mL serum. The function of grafts in the other children was within the normal range and they have a good quality of life.

The difference in levels of graft survival improvement between recipients of living related and unrelated kidneys became apparent only after one year and continued thereafter. The Kaplan-Meier survival curve shows this difference between the two groups (Fig. 1).



Time after renal transplantation

**Fig. 1.** Graft survival.



Time of renal transplantation (months)

**Fig. 2.** Graft survival and kind of living donor-recipient.

Fig. 2 shows the graft survival rates for 1, 2, and 5 years. Survival rates of patients were 100% and survival rates of grafts following 1, 2, and 5 years were 95%, 83%, and 72% respectively. Overall outcome following this ten year period is 62% (Fig. 2).

**DISCUSSION**

End-stage renal disease is managed by four techniques: hemodialysis, peritoneal dialysis, cadaveral, and living donor transplants. The challenges are to prevent death and improve the quality of life so that the patient can achieve normal psychological mental and physical development. In adults the advantages and disadvantages of dialysis versus transplantation are constantly changing, but no such debate is necessary in pediatric renal transplantation, because all

dialysis modalities lead to a deceleration of growth and cause osteodystrophy, central nervous system morbidity, and psychological problems.<sup>18,21,16</sup> Successful transplantation, however, typically results in dramatic improvement of all aspects of physical, emotional and social functioning.<sup>12,21</sup> Importantly, cognitive skills improve, suggesting stabilization of neurophysiologic functioning.<sup>19</sup> Quality of life measures have demonstrated excellent rehabilitation in long-term survivors after successful renal transplantation.<sup>17,22,1</sup>

In Khorasan province of Iran there are 14 hemodialysis centers, but only one is a pediatric center. The pediatric hemodialysis center is in the capital of the province, thus making it difficult for small children from the outlying regions in the province to take advantage of these services.

In Imam Reza Hospital from 1989 to 1999, 51 renal transplantations were performed on 49 children (2 repeats). Until three years ago, out center lacked hemodialysis facilities for small children. Thus renal transplantation was performed on 8 children with ESRD without prior hemodialysis.

Reconstructive surgery and nephroureterectomy prior to renal transplantation is more common in pediatric recipients than in adult recipients because children have more lower urinary anomalies, such as uretero-vesical reflux, urinary diversion due to posterior urethral valve and neurogenic bladder.<sup>2,14,7</sup> In 2 children we performed augmentation cystoplasty with dilated ureter, and in one child, we used a sigmoid segment due to neurogenic bladder with small capacity. Bilateral and unilateral nephroureterectomy were done in 5 children due to high grade ureterovesical reflux with persistent urinary tract infection before transplantation or during renal transplantation.

The principles of surgery in pediatric recipients is the same as in adults.<sup>15,3</sup> In small children weighing less than 15.2 kilograms, however, the adult donor kidney was inserted intraperitoneally, and in such recipients careful attention must be paid to the hemodynamic response upon clamping and unclamping the major vessels.<sup>12,13</sup> It is desirable to maintain a central venous pressure (CVP) above 15 to 18 cm H<sub>2</sub>O before unclamping.<sup>4</sup> Perfusion of the transplanted kidney may be slow because a large adult kidney will take up a significant portion of the normal pediatric blood volume.

Hemodynamic studies suggest that the cardiac output of infants must double to perfuse the adult donor kidney adequately.<sup>3,5</sup> Thus, volume replacement is critical. In our center, we induced over-hydration during vascular anastomosis and tried to raise the systolic blood pressure more than 120 mmHg, just before releasing the vascular clamp.

The immunosuppressive regimens used in pediatric and adult renal transplantation are similar, but there are some differences in drug dosages, because children have less intestinal surface areas, increased rate of metabolism and the need for growth.<sup>4,21</sup> As compared to adults, children require higher or more frequent dosages of oral cyclosporine.<sup>25,24,16</sup>

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In our center we did not administer cyclosporine to 6 children because they received grafts from HLA identical donors. Azathioprine and prednisolone were administered to all recipients. Acute rejection was treated by high doses of methylprednisolone, and in cases of methylprednisolone resistance, antilymphocyte globulin was used. The rate of acute rejection in our center was 21%; all responded to pulse therapy.

After release of the vascular clamp, immediate function of the transplanted kidney is demonstrated by the production of urine. The most common cause of immediate graft nonfunction is acute tubular necrosis (ATN).<sup>3,24,10</sup> In all 51 transplantations, we had immediate diuresis and no occurrence of ATN. Data from the NAPRTCS 1996 Annual Report show that ATN is observed in 5% of living donors and 19% of cadaveral donor transplantations.<sup>18</sup> Early acute rejection can mimic ATN or co-exist with it. The presence of ATN has adverse effects on the outcome of the graft.<sup>5,13,24</sup>

Daily corticosteroid therapy may have adverse effect on growth, with some children failing to attain an accelerated growth rate.<sup>18</sup> Some data shows alternate-day corticosteroid therapy can result in accelerated growth in some patients, especially in young recipients with good allograft function.<sup>6,23</sup> The rate of acute rejection between patients receiving alternate-day and daily corticosteroids is similar.<sup>6,2,5</sup> In our study, 15% of children continue to have growth retardation after renal transplantation. The cause of this problem may be a consequence of daily corticosteroid administration or in some cases due to inadequate graft function. We evaluated the cause of graft and patient losses in our center. We had no patient loss in children; there was no graft loss due to technical problems. The main causes of graft loss were chronic rejection (8.5%), followed by recurrence of the original disease (2%). Among patients who lost the graft, 98% returned to dialysis and thus far 2 children have been retransplanted; one retransplant was performed one year following the original transplantation and the other, one and one half years following the original transplantation.

With increased length of follow up, chronic rejection continued to increase. NAPRTCS data shows that 28% of the causes of graft loss are due to chronic rejection with the second most prevalent cause being recurrence of the original disease, especially focal segmental glomerulosclerosis and membrane proliferative glomerulonephritis.<sup>16,24</sup>

NAPRTCS data shows that graft survival for index transplants at 1, 2, and 5 years (live donors) are 90%, 86%, and 76% respectively.<sup>24</sup> In our center, the corresponding rates are 93%, 83% and 72%.

Successful transplantation markedly improved the emotional and social well-being of the child and his or her family.<sup>8,21</sup> About six months following transplantation when medications, biochemical monitoring and visits to the physician are reduced and the child is under fewer dietary constraints and less parental supervision, the family's routine

becomes more manageable.<sup>9,22</sup>

Several months or years after renal transplantation, side effects of medications, such as Cushingoid appearance, obesity, gingival hypertrophy, acne and hirsutism may appear, which are important to the perception of body image, especially for adolescent girls and may adversely influence medical compliance and lead to graft loss.

Medical noncompliance is prevalent in forty-three to fifty percent of the pediatric transplant population and is believed to account for about twenty-five percent of pediatric allograft losses.<sup>24,11</sup> We could not determine the true prevalence of medical noncompliance in our center, but we understood that there was a higher incidence of noncompliance among adolescent girls living in rural areas, with unstable or poor family backgrounds, and receiving low supervision.

In conclusion, by all measures, renal transplantation is still the treatment of choice for children with ESRD. Pediatric renal transplantation can be done with acceptable morbidity, a low rate of technical complications and low mortality, and thus improved quality of life.

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