Pediatric Renal Transplantation: 13 Years of Experience—Report From The Chilean Cooperative Multicenter Group

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ABSTRACT

Between 1989 and 2002, 178 renal transplants were performed in 168 pediatric patients in Chile. The mean age was 10.9 ± 3.7 years (range 1 to 17.9). End-state renal disease etiologies were: congenital renal hypoplasia/dysplasia, chronic glomerulonephritis, and reflux nephropathy. Seventy received a graft from a living donor (LD), and 108 from a cadaveric donor (CD). Only 9% received antibody induction. Acute rejection episodes were reported in 76 patients: 38% in LD recipients and 48% in CD recipients (P = NS). One-, 3-, and 5-year graft survivals were 88%, 84%, and 76%, respectively, for LD and 86%, 79%, and 68% for CD recipients. Actuarial graft survival was significantly better among those patients with serum creatinine < 1 mg/dL at 1 year posttransplant compared with those with creatinine > 1 mg/dL (P < .05). The graft survival rate has improved from the first period (1989 to 1996) to the second period (1997 to 2002); (P = .05). Patient survival rates at 1, 3, and 5 years were 98%, 98%, and 98%, respectively, for LD, and 95%, 94%, and 94% for CD. Global height/age Z-score decreased from -0.7 at birth to -1.5 when dialysis started, and to -2.4 at the time of transplantation. The Z-score height/age at 1, 3, and 5 years posttransplantation was -2.25, -2.24, and -2.5. No significant differences were observed in transplant outcomes comparing patients younger than 7 years with those older ones. In conclusion, pediatric renal transplant has been performed in Chile with acceptable morbidity. The patient and graft survivals are similar to the reported international experience. In the last period there was a significant improvement in graft survival.

RENAL TRANSPLANTATION is recognized as the therapeutic procedure of choice in pediatric patients with end-stage renal disease (ESRD), based on the improvement in the quality of life and the rehabilitation it provides.[1–3]

In the past few decades, patient and graft survivals have significatively improved, due to technical advances and new immunosuppressive drugs.[4,5] Collaborative studies have been of major importance for the better management of pediatric renal transplant patients.[4–6] In Chile approximately 240 renal transplants are performed annually, with 15% in pediatric patients. The numbers are constantly increasing, both for total number and proportion of pediatric patients.[7] To evaluate the results of pediatric renal transplantation in our country, three public pediatric hospitals started a registry that follows 80% of children who receive a renal graft in Chile.

PATIENTS AND METHODS

Information on renal transplants performed between July 1989 and July 2002 was collected at three centers, considering three items:

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demographics (gender, age, original disease leading to ESRD, type of dialysis); transplantation characteristics (type of donor, cold ischemia time, HLA of both recipient and donor, immunosuppressive therapy, acute rejections, graft and patient survival, graft function, complications); and growth rate (from birth, the beginning of dialysis, the time of transplantation, and during posttransplantation follow-up).

The variables were expressed as mean values ± standard deviations; growth was expressed as height/age Z-score. Renal function was evaluated using serum creatinine levels. Data were organized to provide analyses of graft survival and the relationship of these endpoints to variables such as graft source, degree of HLA mismatch, and graft function. Standard univariate and multivariate statistical methods were used for data analysis. Acute rejection episodes (AR) related to living donor (LD) or cadaveric donor (CD) were analyzed with the Chi square or Pearson's correlation test. Graft and patient survival rates were estimated using the Kaplan-Meier method. The level for significance was $P < .05$.

RESULTS

Between 1989 and 2002, 178 renal transplants were performed in 168 patients: 10 patients (5.6%) received two grafts each. Table 1 shows some recipient characteristics. Mean age was 10.9 ± 3.7 years (range 1 to 17.9 years). The more frequent original diseases leading to ESRD were congenital renal hypoplasia/dysplasia, glomerulonephritis, and reflux nephropathy. Only 10% of patients received no dialysis therapy before transplantation.

For donor source; 70 (39%) were LD and 108 (61%) CD. During the first period (1989 to 1996), 60 renal transplants were performed; 32 (53%) LD and 28 (47%) CD. During the second period (1997 to 2002), 118 renal transplants took place; 38 were LD (32%), and 80 were CD (68%).

The mean cold ischemia time was 23 (±7) hours: in 64 patients (59%), it was 24 hours and the longest one was 44 hours. HLA mismatch (MM) was 30% for three HLA MM and 10% for one MM. Induction immunosuppressive therapy included polyclonal or monoclonal antibodies in five patients (3%) and anti-CD25 antibodies in 10 patients (6%).

Most children received steroids ($n = 178$, 100%); calcineurin inhibitors (171, 96%); azathioprine ($n = 143$ recipients, 80%), or recently MMF ($n = 35$ patients; 20%). Among the calcineurin inhibitors, most patients received cyclosporine. Seventy children were switched to alternate-day prednisone after the first posttransplant year. A first acute rejection episode was reported in 76 patients: 38% (25/70) in LD and 48% (51/108) in CD ($P = $ NS).

Regarding graft function, the mean serum creatinine levels (mg/dL) at 1, 3, and 5 years posttransplantation were 1.0 ± 0.6, 1.3 ± 0.6, and 1.3 ± 0.7, respectively. The graft survivals at 1, 3, and 5 years posttransplantation were 88%, 84%, and 76% for LD, and 86%, 79%, and 68% for CD (Fig. 1). Graft loss occurred in 44 of the 178 recipients (25%) at 12 months. The reasons for graft losses were: 11 noncompliant patients, nine vascular thromboses, seven chronic rejections, five acute rejections, two relapses of original glomerulonephritis, two primary graft nonfunction-

Table 1. Demographic Characteristics of 168 Primary Transplants

	n	%
Gender		
Male	89	53
Female	79	47
Age (y)		
0–1	2	1
2–5	16	9
6–12	102	57
>12	58	33
Primary diagnosis		
Hypodysplasia/dysplastic kidney	34	20
Focal segmental glomerulosclesrosis	10	6
Other glomerulonephritis	23	14
Reflux nephropathy	32	19
Obstructive uropathy	22	13
Hemolytic uremic syndrome	14	8
Other	33	20
Preemotive transplants	18	10
Maintenance dialysis prior		
Hemodialysis only	53	30
Peritoneal dialysis only	86	48

ing and nine deaths with a functioning graft. At 12 months posttransplantation graft survival was significantly better among the group with serum creatinine levels lower than 1 mg/dL versus the group with values over 1 mg/dL ($P < .05$). No significant graft survival differences were observed for variables of donor source ($P = .42$), acute tubular necrosis (defined as the need for posttransplantation dialysis; $P = .27$), cold ischemia time shorter than or higher than 24 hours ($P = .78$), or mismatch for HLA-A ($P = .65$), HLA-B ($P = .41$), or HLA-DR ($P = .80$).

The functional graft survivals at 1, 3, and 5 years in the first period evaluated were 85%, 81%, and 63%, increasing to 87%, 86%, and 78% during the second period ($P = .05$).

The patient survivals at 1, 3, and 5 years were 98%, 98%, and 98% for LD, and 95%, 94%, and 94% for DC. The causes of death were mainly infectious (four bacterial, two CMV, two fungal) and one arrhythmia.

Urinary tract infections (UTI) were the most common site, occurring in 36 patients (20%). Recurrent UTI occurred in more than half of the cases, while CMV infection was diagnosed in 29 patients (16%).

The most common noninfectious complication was vascular thrombosis with 11 cases (nine of whom finally lost the graft), followed by vesicoureteral reflux ($n = 9$), lymphocele ($n = 5$), urethral obstruction ($n = 4$), renal lithiasis ($n = 2$), urine leak ($n = 2$), and renal artery stenosis ($n = 1$).

Only one malignancy was diagnosed: a gastric lymphoma detected during the 7th year posttransplantation. Following partial gastrectomy, the patient had an uneventful recovery, without losing the graft. The global linear growth of this group of patients, expressed in Z-score height slowed from −0.7 at birth to −1.5 at start of the dialysis ($P < .05$) and to −2.4 at the time of transplantation ($P < .05$). The Z-score

heights at 1, 3, and 5 years posttransplantation were −2.25, −2.24, and −2.5. No significant difference was observed in the posttransplant outcome comparing patients younger versus older than 7 years (Fig 2).

DISCUSSION

This multicenter study represents the second evaluation of pediatric renal transplantation in Chile,[8] including over 80% of cases. The number of transplant recipients more than doubled during 1997 to 2002 compared with the previous period (118 patients versus 60). Thus transplant activity is increasing. The proportion of male-to-female recipients has remained stable over time, as well as the median transplant age (10.9 ± 3.7 years). However, the range has increased, incorporating infants less than 24 months old.

In terms of diagnosis, we observed a much greater incidence of reflux nephropathy than the NAPRTCS[5]; nevertheless, it had decreased from our previous report.

The proportion of LD and CD increased significantly from 47% during the first period to 68% in the second one. Our results differ from the last report of NAPRTCS,[5] showing an important increase in LD. This reflects the good results of cadaveric organ donation in Chile.[7] Our patient and allograft survivals are comparable to the published international experience.[5] Only serum creatinine below 1 mg/dL at 12 months posttransplant correlated with a good prognosis of graft survival.

Most patients in our study received immunosuppressive therapy based on cyclosporine, prednisone, and azathioprine. Only 10% of patients received polyclonal or monoclonal anti-IL2 receptor antibodies for induction therapies. A few were prescribed mycophenolate which has recently replaced azathioprine, because of its effectiveness to prevent AR,[9] reverse steroid-resistant ones, and prevent late graft dysfunction.[10,11] Given the multiplicity of currently available immunosuppressive agents and protocols, therapy is presently tailored to individual needs.[1,2]

Corticosteroids have a central role in transplantation. However, they exert important side effects in transplanted children, particularly growth retardation. Thus, efforts have been made to withdraw or lower steroid doses. Alternate-day dosing may partially reduce steroid side effects. At the present time several protocols incorporate new immunosuppressive agents, such as tacrolimus combined with either sirolimus or MMF, to facilitate steroid withdrawal.[12] In our series, 70 patients used alternate-day steroids, a number that may be further increased using new immunosuppressive protocols.

Induction therapy, using antibodies against IL2 receptors, has recently been incorporated in immunosuppressive protocols. Their induction effect takes place mainly during the initial 8 weeks following transplantation, the period of the greatest acute rejection risk.[13]

The rate of AR in our recipients was 42%. The new immunosuppressive agents are critical to prevent AR over
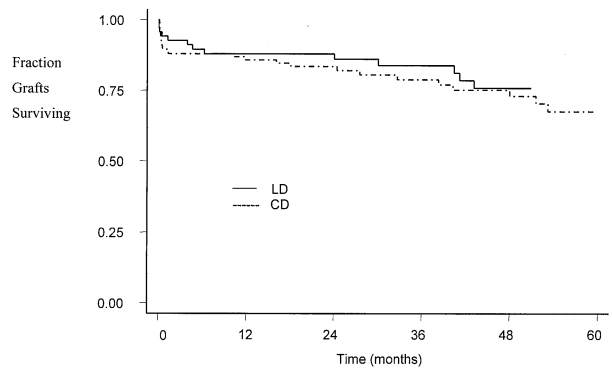

Fig 1. Graft survival rate (Kaplan-Meier) by donor source.

the lifetime of the allograft. The last NAPRTCS report showed that the incidence of AR during the first year among children transplanted from 1987 to 1989 was 60%, while from 1997 to 1999 it fell to only 29%.[5] Using the new antibodies some centers have reported AR rates as low as 5% to 15%.[14−16]

The leading causes of allograft failure are immunological (acute and chronic rejection), noncompliance, and vascular thrombosis. Transplantation age has been identified as an important outcome predictor. Infancy is the group most commonly associated with increased risk, owing to the higher rates of rejection and technical complications. The immediate posttransplant period is the most critical time. However, another important, but less recognized, group at high risk for AR and graft failure is adolescents. The real magnitude of the problem is not known. In 1991, Ettenger et al reported that 50% of 70 pediatric kidney transplant recipients treated with cyclosporine for 6 months or longer showed some degree of noncompliance with 64% being adolescents.[17] Noncompliance with the immunosuppressive therapy has been associated with AR, late AR, chronic rejection;[18,19] as well as graft loss. NAPRTCS in their 2001 Annual Report showed that adolescents have the lowest long-term graft survivals both for LD and CD.[20] The UNOS report shows similar results.[21] During adolescence changes in body image take place, in addition to the normal
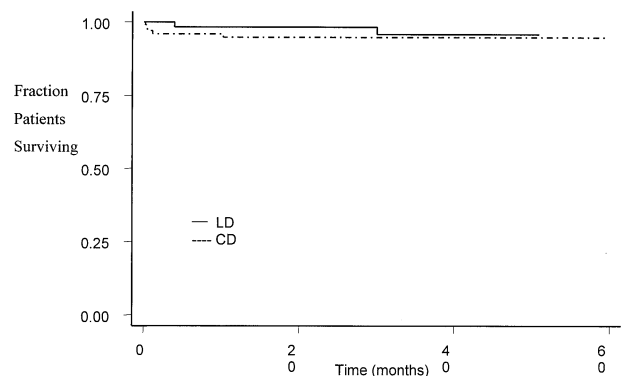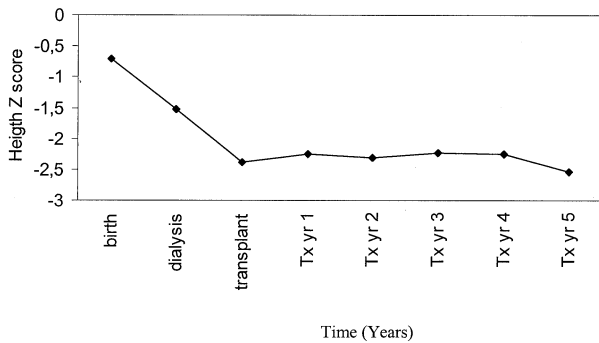

Fig 2. Patient survival rate (Kaplan-Meier) by donor source.

Fig 3. Mean Z-score for height from birth to 5 years posttransplant.

adolescent issues of maturation and psychological changes. Transplant patients are affected by the side effects of immunosuppression (weight gain, cushingoid features, growth retardation caused by steroids, gingival hyperplasia, and hirsutism associated with cyclosporine. The impact of these effects, added to those from the immunosuppressive therapy; makes adolescents an easy target for noncompliance.[22]

Our finding of 25% of noncompliance as the cause of allograft failure contrasts with the lower incidence of NAPRTCS, which may be an underestimation.[5] Our incidence of chronic rejection was 16%, compared with 32.5% in NAPRTCS. We think that this confirms the possibility of underdiagnosis of noncompliance by NAPRTCS, being reported as chronic rejection. Thus, risk factors for adolescents must be identified to obtain optimal immunosuppression and simplify the protocol for optimal long-term graft survival. The 11 patients who lost the graft for this reason were older than 12 years, and most lacked family support.

Vascular thrombosis was the third cause of graft failure, namely 6% (11/178) of recipients. Most events occurred during the first period (prior to 1996). The risk of graft thrombosis may be increased by several factors: peritoneal dialysis prior to transplantation, cadaveric donors less than

5 years old, recipients less than 2 years of age, repeated transplantations, and cold ischemia time over 24 hours.[23–29] The NAPRTCS database also reported that the higher number of transplants in a center correlated with a lower incidence of graft vascular thrombosis.[30]

Infections were the main cause of death. NAPRTCS reported an increasing number of hospitalizations for this reason, with 34% of deaths resulting from infections.[5] Probably stronger immunosuppression is an important factor. Thus, monitoring and prophylactic protocols must be continuously reviewed.

Lower linear growth is also important: the fall of Z-score of −0.7 at birth to −1.5 at the start of dialysis to −2.4 at the transplantation reflects the impact of uremia on growth (Fig 3). Following transplantation, the Z-scores for the stature at 1, 3, and 5 years were of −2.25, −2.25, and −2.5, respectively, showing that although there was no further deterioration, growth did not improve (Fig 4). Comparing the stature progress in prepubescent recipients less than 7 years of age with children older than 7 years, we did not observe any trend toward better Z-scores among the younger group. NAPRTCS 2002[5] reported that only patients transplanted at younger than 6 years of age showed accelerated or catch-up growth. This observation could not be evaluated in our patients, since only 9% were younger than 6 years.

Nevertheless, the important fall in linear growth seen in our patients prior to dialysis entry and also our observations regarding growth and transplant age lead us to conclude that transplantation must be performed early, since once the growth potential during the first 5 years of life is lost, the stature deficit is never recovered.

In summary, this report reviewing pediatric renal transplantation in Chile during the last 13 years confirms that renal transplantation can be performed with low morbidity and with graft and patient survivals similar to those reported in the international experience. During the recent period we have observed even improved graft survival. Growth retardation and noncompliance remain important
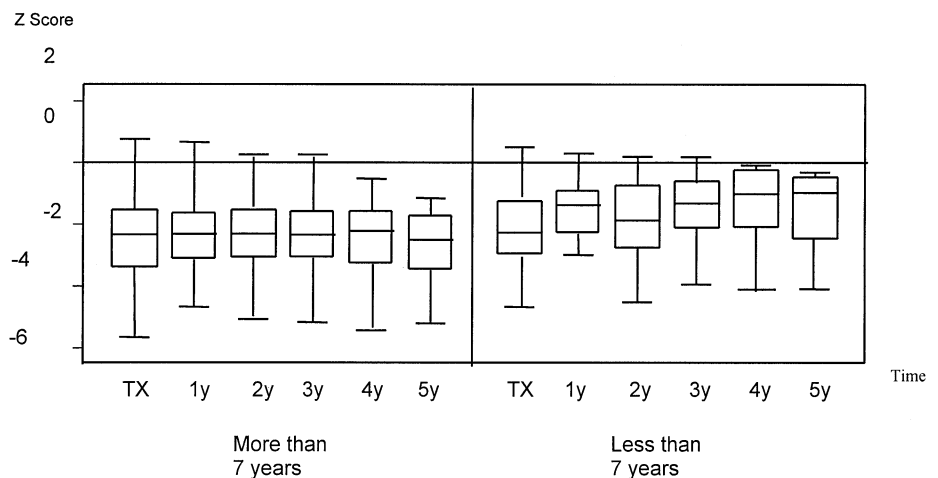
Fig 4. Mean Z-score for post-transplant height by age at time of transplant.

problems for us. We are convinced that multicenter trials at our institutions will enable us to address these problems.

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