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Kidney transplantation using paediatric kidneys from very young donors

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ABSTRACT

The use of paediatric deceased kidneys is a valuable means to increase the pool of organs for transplantation. However, the choice of single or *en bloc* kidneys remains controversial because of post-operative complications and long-term graft survival. We aimed to evaluate the results of our Transplant Unit using either single or *en bloc* paediatric grafts for transplantation.

Between 1987 and 2008, 18 patients received a graft from a paediatric donor aged ≤8 years. Eleven patients were female (61%), average age 34.1±15 years and 13 (72.2%) were Caucasian. Nine donors were male (50%), average age 5.3±1.7 years and average weight 20.2±7.5 kg. Five patients were transplanted with an *en bloc* graft (9.6%). Five patients (9.6%), all recipients of single kidneys, had delayed graft function secondary to vascular and urological complications. In the long-term follow-up, 5 patients (27.7%) lost the graft to chronic rejection. The graft survival at the first, third and fifth years posttransplant were 94.4%, 94.4% and 81.2%, respectively. Graft survival stratified according to the type of graft received was similar for both single and *en bloc* grafts at the third (92.3% versus 100%, respectively; p=0.061) and fifth year posttransplant (77% and 100%, respectively; p=0.157).

We concluded that, in this small cohort of patients, the use of *en bloc* kidneys was safe and not associated with increased rate of complications or reduced graft survival.

Key-Words:
En bloc graft; kidney transplantation; outcomes; paediatric deceased donor; single graft.

INTRODUCTION

The gap between organ procurement and supply has led to the increased use of organs from paediatric donors to increase the pool of kidneys available for transplantation[1]. Depending on donor age, kidney size and the experience of the transplant centre, paediatric kidneys may be transplanted *en bloc* or as single kidneys, with the former option requiring a more laborious surgical technique. Studies in paediatric organ donation consider, however, that harvesting may be dependent on several factors such as the presence of a paediatric critical care medicine physician or trauma emergency department able to more easily recognise potential donors[2]. Even under these conditions, consent rates above 60% or higher in older children[2] have recently been reported and results with organs donated after cardiac death in paediatric critical care settings are also described[3,4].

However, the use of kidneys from deceased paediatric donors has long raised controversies over

immediate complications and long-term outcomes. Initial reports documented higher rates of surgical complications and reduced tolerance to graft dysfunction episodes[5]. Poorer graft survival[1,6], higher rate of urinary leaks[1] and graft thrombosis[7] or need of a specialised surgical centre to obtain good results[8] are some of the limitations reported in the literature. However, more recently, results of long-term follow-up of recipients of single paediatric kidneys from very young donors found satisfactory results as compared with those from older donors[9], even for *en bloc* paediatric kidney recipients[10].

We aimed to evaluate the long-term experience of our Transplant Unit using paediatric donor kidneys, either single or *en bloc*, and to search for factors associated with poor outcome in this setting.

PATIENTS AND METHODS

Between 1987 and 2008, 18 transplants using grafts from donors aged ≤8 years old were performed in our Unit, but an additional 34 transplants were performed with grafts from recipients between 9 and 17 years old.

Donor data was provided by the regional entity responsible for the distribution of organs for transplantation and information available included sex, age and weight and cause of death whenever available.

The kidneys and ureters were harvested with donor aorta and inferior vena cava as previously described[11] and preserved with flushing solution, mainly Wisconsin solution, and cold storage. Thirteen patients (72.2%) received a single kidney and five patients (27.7%) two or an *en bloc* graft. In donors aged 8 or over, the graft was supplied to the surgical team as a single kidney. In donors under 8 years old, kidneys were usually provided *en bloc* and the decision to transplant one or both grafts was usually undertaken by the surgeons taking into account surgical and technical aspects of both the graft and the recipient (size of the kidneys, body mass index of donor and recipient, length and number of arteries in the graft, previous transplant or presence of advanced atherosclerotic disease of the iliac arteries). All the transplants with the *en bloc* grafts were performed after the year 2001 and prophylaxis with low molecular weight heparin was employed in these cases.

The immunosuppressant protocol varied greatly between patients according to the immunological risk and types of medication available. Ciclosporin, mycophenolate mofetil and prednisone were used in 9 patients (50%) or, alternatively, azathioprine in 6 patients (33.3%). Only 2 patients (11%) were treated with tacrolimus and basiliximab and anti-T-lymphocyte immune globulin were used in 4 (22.2%) and 1 (5.5%) patients, respectively, as part of the initial immunosuppressant schema. In one patient with previous history of haemolytic uraemic syndrome calcineurin inhibitors were not employed. For patients receiving *en bloc* grafts the most frequent immunosuppressant scheme consisted of ciclosporin (four patients), mycophenolate mofetil and prednisone (five patients).

Patients were followed-up from the date of transplant and data on recipients demographic and clinical characteristics, transplant surgery procedure and postoperative period follow-up were obtained. In particular, data on HLA mismatches, cold ischaemia time, delayed graft function (defined as the need for dialysis after receiving a kidney transplant[12]) and immunisation status for cytomegalovirus (CMV) infection was registered. The number of renal arteries for each graft was also registered whenever available.

In the long-term follow-up, kidney function was routinely evaluated according to the Unit's protocol by serum creatinine and urinary creatinine clearance. For the purpose of our analysis, however, only values of serum creatinine at the first month posttransplant and at the end of the first, third and fifth years were obtained. Glomerular filtration rate (GFR) was retrospectively determined by the Modified Diet in Renal Disease equation but paediatric recipients were excluded. Graft dimensions, obtained by abdominal ultrasonography and expressed in centimetres (cm), at the time of transplantation were available for 13 patients. Longitudinal diameter was registered and subsequently compared with the values obtained in the last ultrasonographic evaluation.

In patients transplanted with *en bloc* kidneys the greatest longitudinal diameter of both kidneys was chosen. Causes of graft loss were also identified. The average time of follow-up since the date of transplant

until the date of our analysis or graft loss was 7.7±4.1 years.

To evaluate for differences in outcomes according to the type of graft received, patients were divided in two groups (single *versus en bloc* kidneys).

For the statistical analysis paired *t*-test, Mann-Whitney test and Kaplan-Meyer survival analysis were performed using SPSS 17.0 software analysis. The level of significance was defined for levels of $p<0.05$.

RESULTS

Between 1987 and 2008, the cohort of paediatric donors (≤ 17 years old) in this Transplant Unit consisted of 52 children, of which 18 (34.6%) were ≤ 8 years old. Of these donors, nine were male (50%), average age 5.3±1.7 years and average weight 20.2±7.5 kg (weight was available only for 8 donors). The youngest donors were two years old (two patients). The main causes of death were brain death secondary to cranial trauma (61%) and sink (11%), and in none of the donors was death attributed to cardiac death.

Overall, three grafts were transplanted into three paediatric recipients with ages ranging from 7 and 17 years, but none of the paediatric recipients received *en bloc* kidneys. In two cases patients underwent a second transplant, but only one with an *en bloc* graft. None of the patients underwent preemptive transplantation. The average recipients' age was 34.1±15 years; they had been on dialysis for 29.6±24.9 months (minimum 6.2; maximum: 85 months) and on the waiting list for 18.5±16.5 months (minimum 3.9; maximum 45.3 months).

Fourteen patients (77%) had three or more HLA mismatches with the donor and the average cold ischaemia time was 16.4±4.2 hours. Table I presents the main clinical and demographic characteristics of recipients of single and *en bloc* grafts.

With the exception of *en bloc* kidneys, only one graft had two renal arteries. Nine patients (50%) experienced some type of complication in the immediate posttransplant period: acute rejection was diagnosed in 4 patients (44%), acute tubular necrosis in 3 (33%) and surgical complications including perirenal haematoma and lymphocele in 2 patients (22%). The rate of complications per single or *en bloc* graft was 53.8% (7 out of 13 patients) and 40% (two out of five patients), respectively. The incidence of acute rejection (antibody-mediated or cellular) was superior in the group of patients that received a single kidney (30.7% or 4 of 13 patients) as opposed to those who received *en bloc* kidneys (0%). However, immediate function of the graft ($p=0.891$), incidence of complications in the post-operative period ($p=0.609$), cold ischaemia time (p=0.909), number of mismatches (p=0.432) and delayed graft function (p=0.891) were similar in patients receiving single or *en bloc* kidneys. The main causes of delayed graft function (22.2% or 4 patients) were acute tubular necrosis (2 patients), acute rejection (1 patient) and also perirenal haematoma in 1 patient receiving a single graft. In none of the patients vascular thrombosis of the graft was observed.

Table I

Clinical and demographic characteristics of recipients of single and *en bloc* grafts.

	Single kidney	*En bloc* kidneys	p
Age	33 ± 16.3	36.8 ± 12.2	0.641
Males	6	1	0.322
Caucasians	11	4	0.933
Weight	51.2 ± 16.1	57.7 ± 6.1	0.407
CMV IgG positive	10	4	0.891
Time on dialysis (months)	28 ± 23.9	36.1 ± 30.8	0.569
Waiting list (months)	19.2 ± 17.2	16.7 ± 16.1	0.783
Donor's age	5.9 ± 1.3	4 ± 2.1	0.032
Cold ischaemia time	16.2 ± 5	17 ± 1.8	0.741
Induction therapy*	5	3	0.423

* Monoclonal or polyclonal antibodies

In the long-term follow-up, 5 patients (27.7%) lost the graft secondary to chronic allograft nephropathy (3 patients), recurrence of primary renal disease (1 patient) and systemic infectious complications (1 patient). One of the patients who developed chronic allograft nephropathy had an *en bloc* graft.

The overall graft survival was 7.7±4.1 years (minimum 2.2; maximum 17.5 years). At the first, third and fifth year posttransplant graft survival was 94.4%, 94.4% and 81.2%, respectively. Two patients

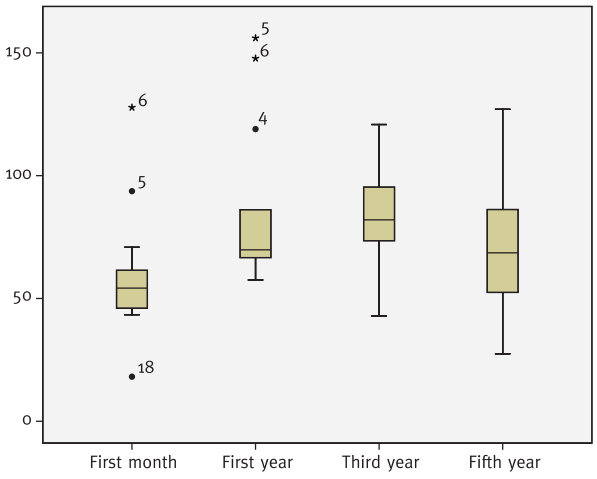

Figure 1

GFR variation at the first month and first, third and fifth years posttransplantation (N=18).

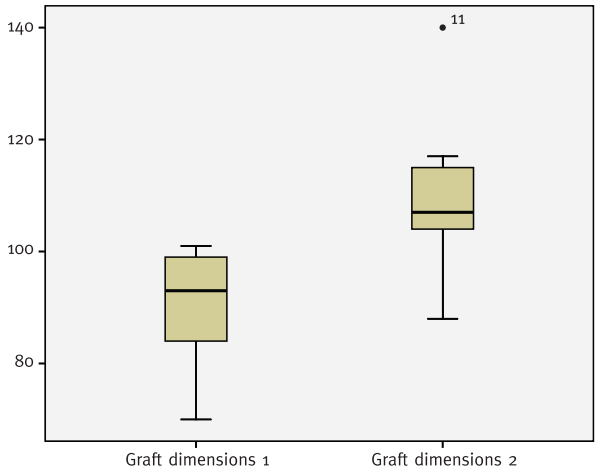

Figure 2

Variation in graft dimensions (in centimetres) between the first (1) and last ultrasonographic evaluation (2).

(11%) died, all with a functioning graft. Graft survival stratified according to single or *en bloc* kidneys was similar at the third (92.3% *versus* 100%, respectively; *p*=0.061) and fifth years posttransplant (77% *versus* 100%, respectively; *p*=0.157).

Figure 1 presents the variation of GFR for all the 18 patients studied. GFR increased significantly between the first month and the first year posttransplant (61.1±29.3 *versus* 88.9±35.4 mL/min/1.73m^2, respectively; *p*=0.000) and remained stable at the third (92.2±34.1 mL/min/1.73m^2; p=0.739) and fifth (71.3±29.3 mL/min/1.73m^2; *p*=0.163) years after transplantation, even if a small decline was observed between these last two determinations. However, when considering the differential GFR of single *versus en bloc* grafts (Table II), a trend toward an increased GFR for *en bloc* kidneys was observed at the first month, first and third years, albeit statistically not significant.

Table I

Quantitative variation of GFR (MDRD) for single and *en bloc* grafts

GFR (mL/min)	Single kidney	*En bloc* kidneys	P
1st month	54.3 ± 24.3	82.9 ± 34.5	0.064
1st year	78.9 ± 32	110.9 ± 35.7	0.095
3rd year	82 ± 21.3	104.1 ± 26.7	0.105
5th year	77.1 ± 30	52.2 ± 19.2	0.211

In forward logistic regression analysis the occurrence of rejection episodes (odds ratio=-0.371, 95th confidence interval -0.416: -0.039; *p*=0.015) and number of mismatches (odds ratio=0.255, 95th confidence interval 0.009: 0.431; *p*=0.030) were the strongest predictors of graft survival one year after transplantation but at the third year only the episodes of rejection remained predictive of graft loss (odds ratio=0.422, 95th confidence interval 0.150: 0.711; *p*=0.019).

An increase in graft dimensions between the first measurement posttransplant and the last ultrasonographic evaluation performed was documented (Figure 2). The average longitudinal diameter in the first evaluation was 9.1±1.1 cm and at the last examination 10.8±1.5 cm (*p*=0.003).

DISCUSSION

In our cohort of patients, the use of *en bloc* kidneys was not associated with either an increased rate of complications or a reduced long-term survival of the graft. Moreover, the use of grafts from paediatric donors resulted in good long-term outcomes, comparable to those described for patients receiving a graft from an adult donor.

For a long time, the use of grafts from paediatric donors was viewed with great uncertainty. Results from retrospective analysis documented higher rate of urological complications, like ureteral fistulas[13], vascular thrombosis[7] and poorer graft survival[6,14,15]. Specifically, results with grafts from very young donors were very disappointing, with reduced survival[15]. Furthermore, the increase in age and weight of donors was associated with better outcomes[6]. Possible reasons to explain these adverse results included the greater incidence of surgical complications because of the reduced size of the donor kidneys and greater impact of rejection episodes in the graft before it completed the process of growth and hypertrophy after the transplant[16].

However, subsequent reports demonstrated the feasibility and safety of transplants using this kind of grafts[10,11,16-18], allowing more widespread use of these organs. In our cohort of patients, we haven't observed increased rate of surgical complications in the immediate postoperative period or reduced survival as compared with grafts from older donors. Nevertheless, many others have also speculated about the role of donor's age in renal transplantation outcomes and, in particular, about the use of *en bloc* grafts in these circumstances. When considering very young donors, already with mature tubular renal function but yet with reduced renal mass, transplantation of *en bloc* kidneys provides to the recipient greater renal functional mass to accomplish fluid and electrolyte homeostasis and deal with the acute aggressions like acute tubular necrosis or rejection. In addition, avoiding the manipulation and suture of the small vessels of the donor graft may prevent known complications like vascular thrombosis or subsequent renal artery stenoses[11]. In our experience, *en bloc* kidneys were harvested only from very young donors and in the long-term follow-up only one patient lost the graft but not due to vascular or urological complications. Grafts transplanted *en bloc* had a survival rate analogous to that observed in recipients of single kidneys from donors of similar ages and the type of complications was also very similar to that observed in patients receiving a graft from an adult donor.

The evolution of GFR according to the type of graft demonstrated that, as expected, patients receiving *en bloc* kidneys had higher values of GFR. The observed reduction in the average GFR at the fifth year for double kidneys is probably explained by the reduced number of cases and for the fact that one patient actually developed chronic allograft nephropathy with increasing serum creatinine. While the GFR in paediatric patients receiving a paediatric graft usually improves significantly in the first years after the transplant[19], more detailed data on the evolution of GFR of single or *en bloc* grafts is sparse. If a double graft and a consequently higher creatinine clearance may provide advantages for graft and patient survival remains to be determined. Nonetheless, despite the good results in our Transplant Unit using *en bloc* kidneys, transplantation using these grafts was begun only after the year 2001 and our experience and follow-up is smaller than that with single kidneys.

One of the most common complications referred to paediatric *en bloc* kidneys are urinary leaks[1] or stenoses along the ureters or uretero-vesical anastomosis but, in our series, none of the patients studied developed symptoms or signs suggestive of these. Minor clinical problems might have been overlooked, however, as we have performed a retrospective analysis. Instead, a greater proportion of episodes of acute rejection were observed. Several factors might explain this observation, including the reduced age of the recipients, conferring them an increased susceptibility to rejection episodes, or the use of different immunosuppressant schemes along the years. However, the differences in the acute rejection rates between single and *en bloc* grafts are probably explained by the fact that the transplant of *en bloc* kidneys was performed later, using different pharmacological approaches rather than to differences attributable to the surgical procedure itself or others.

In the posttransplant follow-up, the most important factors for graft survival were the occurrence of episodes of rejection and number of HLA mismatches. However, rejection persisted as the main factor predicting poor survival in the long-term follow-up. While this is not unexpected, it is worthwhile noting that transplantation of *en bloc* grafts was not associated in this statistical model with worse survival and these patients also did not present a greater incidence of delayed graft function.

The major surgical complications reported in our cohort of patients were the perirenal haematoma

and lymphocele and no cases of vascular thrombosis were documented. These are also some of the most frequently documented surgical problems after adult deceased donor kidney transplantation, most of the times not representing threatening conditions for the graft and not implying surgical reintervention. Nevertheless, the reduced number of patients analysed and, in particular, the number of cases of *en bloc* transplantation should be taken into account.

Interestingly, and as reported by others, grafts from paediatric donors retain the capacity to adapt and hypertrophy. This is well demonstrated by comparing graft dimensions at two different points in time, whereby we observed an increase in grafts' longitudinal diameters. In these circumstances two types of renal growth can be observed[19]: an obligatory growth that accompanies the normal process of growing, usually observed when a paediatric graft is transplanted into an adult recipient and a compensatory functional response that adapts to and dovetails with the recipients' homeostasis requirements. In these settings it is expected to observe the two types of renal growth because only paediatric kidneys were transplanted and, in the bulk of cases, to adult recipients.

Conflict of interest statement. None declared.

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