A Comparison of Long-Term Graft Survival Rates Between the First and Second Donor Kidney Transplanted—The Effect of a Longer Cold Ischaemic Time for the Second Kidney

Louise Giblin[a], Patrick O'Kelly[a], Dillie Little[b], David Hickey[b], John Donohue[a], Joseph J. Walshe[a], Susan Spencer[b] and Peter J. Conlon[a,*]

[a]*Departments of Nephrology and* [b]*Renal Transplantation, Beaumont Hospital, Beaumont Road, Dublin, Ireland*
Corresponding author: Dr Peter Conlon, peter.conlon@beaumont.ie

Prolonged cold ischaemic time (CIT) is associated with delayed initial graft function and may also have a negative impact on long-term graft outcome. We carried out a study comparing the long-term graft survival rates between those recipients who received the first of a pair of donor kidneys versus the recipient of the second graft.

Adult kidney transplant recipients who received one of a pair of donor kidneys at our institution between 1989–1995 were included. All recipients received a cyclosporin based immunosupression regimen. Graft survival rates were compared between the 2 groups at 1-, 3-, 5- and 10-year intervals. A total of 520 renal transplant grafts were included in this study. Mean donor age was 35.4 years. Groups were similar for recipient age, gender, number of HLA mismatches, transplant number for that patient and percentage PRA. CIT was the only variable that was significantly different between the two groups; mean of 19.93 h in the first group compared to 25.65 h in the second group. Graft survival rates for the first kidney were significantly better than the second kidney—graft survival at 1 year 88.5% versus 84.7%, at 3 years 81.8% versus 76.7%, at 5 years 72.2% versus 64.9% and at 10 years 55.2% versus 40% (p = 0.012). Patient survival rates were similar in both groups.

In our experience, the long-term graft survival rates are significantly better for the first kidney transplanted compared to the second kidney.

Key words: Acute rejection, cold ischaemic time, delayed graft function, graft survival rate, patient survival rate

Introduction

Over the past two decades, we have seen an improvement in the long-term survival rates for kidney transplantation. There are many factors, which have contributed to this and much of the improvement can be attributed to the developments we have seen in the area of transplant immunosuppression, particularly the introduction of cyclosporin in the mid-1980s. Several other newer anti-rejection agents have since been developed for transplantation. Since the introduction of these newer medications into clinical practice we have seen considerable improvements in both the acute and chronic rejection rates and thus as a consequence of this some authors have reported an improvement in both short- and long-term patient and kidney graft survival rates (1,2). Other factors such as improved organ procurement techniques and better facilities for the transport of the recovered organ have also helped to minimize damage to the donor organ prior to transplantation into the recipient. The time from harvesting the organ from the donor until the graft is implanted into the recipient, the "cold ischaemic time" (CIT) is also known to have an impact on kidney graft survival rates (3,4). A prolonged CIT has been clearly associated with a higher incidence of delayed graft function (DGF) (3–6). Several multicenter studies have demonstrated a clear link between DGF and kidney graft survival in both the short and longer term (4,6–9). However, other single centers have reported data, which directly contradicts this, and claim that DGF is not an independent risk factor for poorer long-term survival rates, but that it may serve as a prognostic marker only when it is associated with acute rejection (AR) (3,5,9–13). We therefore, designed our study to look at the impact of CIT on the long-term outcomes of the kidney transplant recipients at our center. We compared the survival outcomes between the first and the second of a pair of donor kidneys and assessed the effect of a longer CIT for the second kidney group. This unique and unbiased sampling

method provides an alternative approach to analyzing the effect of CIT on graft outcome.

Methods

All renal transplant operations performed in the Republic of Ireland are done at a single center, the National Kidney Transplant Unit at Beaumont Hospital in Dublin. We are not part of any international organ-sharing programme and thus all kidneys that are transplanted in Ireland come from donors within our own country.

Inclusion criteria

For this study we included only adult recipients (age 18 years or greater) of a deceased donor graft. We excluded from the study, 150 adult transplant recipients who acquired the matching kidney of a pediatric recipient from the same donor. We did not include any patients in whom the transplanted organ was a single donor kidney as there was no partner organ available for comparison. All kidney transplant recipients who met the above criteria and who received one of a pair of donor kidneys at our institution from the January 1, 1989 until December 31, 1995 were included in the analysis. Follow-up analysis was to the end of December 2001. The definition of graft failure was date of return to dialysis therapy after transplantation or date of death. Data at the time of transplant and all follow-up data were attained from the Beaumont Hospital Renal Database system and the National Renal Transplant Registry.

At our center a single transplant surgeon performs both of the transplant procedures so that there is generally an average of 6-h delay between the implantation of the transplant organ into the first recipient compared with that of the second. Thus there is a longer CIT for the recipient of the second of the pair of donor kidneys transplanted.

Definition of patient groups

The groups were thus termed "first" and "second" kidney group depending on whether they were the first or the second recipient transplanted. As the study included only cases in which there were a pair of donor organs the two groups were identical for donor details, such as donor age, donor gender and donor cause of death. We also compared the two recipient groups for recipient details such as age, gender, degree of Human Leukocyte Antibody mismatching (HLA mm) and panel reactive antibodies (PRA) percentage. The main reason why a particular patient would receive the first or second kidney was who arrived to the transplant center first and who was ready for theater the sooner. The main reasons for the delay for the second recipient were the distance they had to travel to reach the center and whether they required haemodialysis immediately pre-operatively. In general, the donor kidneys are allocated to the best available HLA match on our transplant waiting list, although some consideration is also given to the duration of time each candidate has been waiting and also age-matching of the recipient with the donor.

Immunosuppression protocols

All patients received a triple therapy immunosuppression regime as were our standard protocol throughout that time period. This consisted of cyclosporin, azathioprine and corticosteroid therapy. AR episodes were treated with intravenous steroid boost and in some resistant cases OKT3. The indications for a renal transplant biopsy were a rise in the serum creatinine of $>/= 15\text{--}20\%$ from the baseline level (in the absence of any other clear clinical explanation) and/or if there was a high index of suspicion of an AR episode.

Storage techniques

During the study period all kidneys were retrieved by *in situ* perfusion in Eurocollins and cold-stored at 4°C. Machine perfusion techniques have not been used at any point in our institution. During the study period we did not have a prospective tissue typing facility available and this delay contributed to the total CIT. All the donor tissue typing and all the transplant crossmatching procedures were carried out locally at our transplantation center. The crossmatching of all potential transplant recipients is done simultaneously.

Statistical analysis

The tests used were Wilcoxon rank-sum for continuous variables and Pearson chi squared for group variables. The short-, medium- and long-term survival rates were compared between the two kidney groups at intervals of 1, 3, 5 and 10 years post-transplant, using Product-Limit (Kaplan-Meier) methods. The same technique was used in analyzing the half-life of the grafts. Modeling methods to predict outcome of transplant related variables were conducted using Cox proportional hazard models. All of the statistical analysis was performed using Stata (version 8, TX). A p-value < 0.05 was considered statistically significant.

Results

There were a total of 520 renal transplant grafts included in the analysis (260 transplants in each group). The mean donor age overall was 35.4 years. The donor sex was 60% male and 40% female donors. The demographic details of the recipients of a first or second kidney are presented in Table 1. Comparing the recipients of both groups reveals broadly similar results between them, indicating a lack of bias in the order of allocating kidneys in terms of age, gender and medical history. The graft CIT was the only variable that was significantly different between the two patient groups. This was a mean of 19.93 h (range 3–42, SD 4.63) in the first kidney group versus 25.65 h (range 12–53, SD 6.32) in the second group giving an average delay of almost 6 h for the second kidney.

As expected, there was a higher incidence of DGF in the second group as they had a longer CIT. This was defined as the requirement for dialysis in the first week post-transplantation. This occurred in 3.8% of first kidneys versus 7.3% of the second kidney group (p = 0.085). We also compared the two groups for AR episodes. AR rates were 22.3% in the first kidney group compared with 28.1% in the second kidney group.

Table 1: Group demographic details

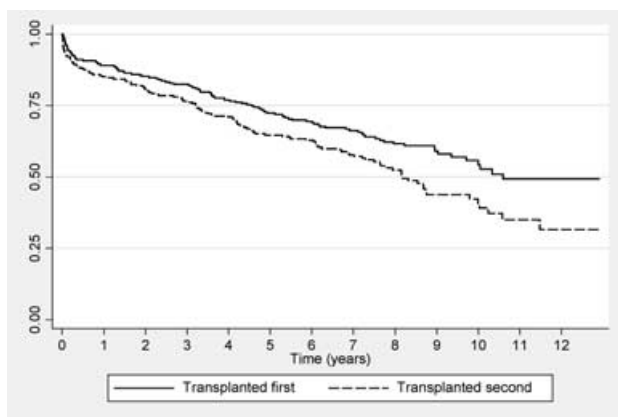| Variable	First kidney group	Second kidney group	p-value
Age in years	42.6	43.3	0.469
Patient sex M:F	165:95	170:90	0.647
PRA (%)	16.38	18.5	0.301
HLA (mm)	2.43	2.59	0.230
Transplant number (First/regraft)	215/45	212/48	0.464

Figure 1: Kidney graft survival rates.

Graft survival rates for the first kidney were significantly better than the second kidney—graft survival at 1 year 88.5% in the first group versus 84.7% in the second group, at 3 years 81.8% versus 76.7%, at 5 years 72.2% versus 64.9% and at 10 years 55.2% versus 40% (p = 0.012). Patient survival rates were similar in both groups. Median graft survival was 10.6 years for the first kidney group versus 8.2 years for the second group. Figure 1 presents the above results in graphical format.

Given that the overall graft survival was significantly better in the first kidney group, the next step was to introduce the demographic variables as presented in Table 1 and to include order of transplant, DGF and AR with these variables in a single model (Table 2). This procedure tested for independence of effect by placing the variable in the presence of other variables that may influence outcome in order to see if statistical significance was still maintained. Using the Cox proportional hazards model, the results clearly demonstrate that significance of increased risk for the second versus the first transplant procedure is retained in the presence of other predictors of outcome. The age of the recipient was also significant (p < 0.001), with male gender and higher percentage PRA levels marginally non-significant at this level. The effects of the first versus the second kidney also remain statistically significant when the data was censored for death with a functioning graft (Table 3). We also substituted the first versus second kidney variable with the actual CIT (in hours) and analyzed the effect this had on the kidney graft outcome (Table 4). In this model, the CIT does not provide the strong significant result that was detected for the former variable.

Discussion

There are many risk factors known to predispose a renal transplant graft to DGF. These include older donor age and delayed or complicated transport of the organ prior to transplantation (4–6,9). It is also widely accepted that a prolonged CIT is associated with a higher incidence of DGF (4–15). Many studies have demonstrated that older donor age and male gender of the donor have an impact on long-term graft survival (3–5,7–9). However, the impact of DGF on the long-term outcome of the renal transplant graft remains controversial. We therefore, undertook this study to examine our experience of patients with a prolonged CIT and the effect this may have on the long-term

Table 2: Multi-factorial model of graft outcome

Variable	Haz. Ratio	SE	z	p	[95% CI]	
Second kidney	1.374071	0.1873595	2.33	0.020	1.051828	1.795037
DGF	1.768262	0.4595599	2.19	0.028	1.06249	2.942852
PRA (%)	1.002356	0.0027371	0.86	0.389	0.997005	1.007735
Recipient age	1.023534	0.0055142	4.32	0.000	1.012784	1.034399
Acute rejection	1.447215	0.2166963	2.47	0.014	1.079145	1.940824
Gender	1.276916	0.1941656	1.61	0.108	0.947828	1.720261
Donor age	1.012945	0.0045762	2.85	0.004	1.004015	1.021954
HLA (mm)	1.020355	0.0548572	0.37	0.708	0.918307	1.133742
Previous trans.	1.095626	0.1766278	0.57	0.571	0.798800	1.502747

Table 3: Multi-factorial model of graft outcome censored for death with a functioning graft

Variable	Haz. Ratio	SE	z	p	[95% CI]	
Second kidney	1.344215	0.1815348	2.19	0.028	1.031609	1.75155
DGF	1.822639	0.5320318	2.06	0.040	1.028568	3.229743
PRA (%)	1.000451	0.0032511	0.14	0.890	.9940997	1.006844
Recipient age	1.000765	0.0064366	0.12	0.905	.9882287	1.013461
Acute rejection	2.029113	0.3479834	4.13	0.000	1.44987	2.839771
Gender	1.21938	0.2236333	1.08	0.279	.8511961	1.746823
Donor age	1.015771	0.0056253	2.83	0.005	1.004805	1.026856
HLA (mm)	1.028673	0.0685931	0.42	0.672	.9026472	1.172293
Previous trans.	1.334742	0.2320377	1.66	0.097	.9493375	1.876611

Table 4: Multi-factorial model with kidney order number replaced with cold ischaemic time (hours)

Variable	Haz. Ratio	SE	z	p	[95% CI]	
CIT	1.0143	0.01266	1.14	0.252	0.9898	1.0395
DGF	1.7444	0.46037	2.11	0.035	1.0399	2.9261
PRA (%)	1.0031	0.00273	1.13	0.260	0.9978	1.0084
Recipient age	1.0243	0.00556	4.43	0.000	1.0134	1.0352
Acute rejection	1.4858	0.22627	2.60	0.009	1.1023	2.0025
Gender	1.2781	0.19651	1.60	0.110	0.9456	1.7276
Donor age	1.0122	0.00462	2.67	0.008	1.0032	1.0213
HLA (mm)	1.0128	0.05529	0.23	0.815	0.9101	1.1272
Previous trans.	1.0943	0.17404	0.57	0.571	0.8012	1.4946

survival of the renal transplant. The baseline donor details were identical for each group and the two recipient groups were also similar in terms of the baseline clinical variables known to impact on long-term graft survival rates. The only clinical variable that was significantly different between the two patient groups was the duration of the CIT, which was obviously longer for the second group. We were able to demonstrate a significant long-term graft survival advantage for the first versus the second kidney with overall graft survival rates up to 10 years post-transplant of 55% versus 40% (p = 0.012).

We feel it is important to emphasize that the decision as to which patient received the first or second kidney was not biased in any way by the recipient age or number of prior transplants that either patient had received. This is evident as the incidences of re-transplants and mean recipient age was similar in both groups. The crossmatching procedures were carried out in parallel and the percentage PRA and HLA mm was similar between the two patient groups. As we already alluded to in the methods section the main determining factor was speed of preparation for theater. The main reasons for the delay for the second recipient were the distance and time taken to reach the transplant center and also whether the patient required emergency haemodialysis in the immediate pre-operative period.

The evidence for CIT as a predictor of graft outcome is not as strong when adapted in its simplest form, which is in analyzing the impact of each additional hour of CIT on the risk of graft failure. The approach that we adopt is based on the higher average CIT between the two groups, and is therefore not identical to analyzing CIT as a predictor variable of graft outcome. The strength of the former variable compared to the latter is explained by the fact that analysis of the former variable is based on the difference of a 6-h CIT between the two groups, in comparison to the latter, which analyses the effect of each additional hour of CIT. The difference in CIT between the two groups is the predominant reason for the difference in graft outcomes detected. We believe that other factors, which may distinguish the two groups such as, fatigue of the surgical team for the second procedure to have a minor effect.

There was an increased incidence, though marginally not significant (p = 0.085), of DGF for the patients in our study who received the second kidney and thus had the longer CIT. The incidence of DGF in our study was low by international standards. This is largely due to the fact that we have a relatively low average CIT. We use only donors that come from within Ireland and as we are a small country the distance to travel for those organs is relatively short compared to other larger countries with a larger geographical catchment area. Furthermore, in this study almost 50% of the transplanted kidneys actually came from donors that were in-patients within the transplanting hospital. The higher incidence of DGF for the second kidney group may have contributed to the negative long-term graft survival rates for this group. The graft half-life for a transplant with DGF in this study was 3.56 years versus 9.9 years for those who had immediate graft function.

AR has been recognized as a predictor of long-term graft outcome in many studies (7,8,10). Analysis of AR rates in our patient group showed a higher incidence of AR in those with the longer CIT. Biopsy-proven AR occurred in 22.3% (58/260) of the first kidney group as compared with 28.1% (74/260) of the second kidney group. Thus the higher AR rate likely contributed to the poorer long-term outcome for the second group. Further analysis of our data revealed that if the recipient developed DGF they were also more likely to subsequently develop AR—47% of those with DGF also had a least one episode of AR.

Our patient groups were very similar in all clinical variables except the difference in CIT. This was an average of 6 h extra delay for the second kidney group. Our data clearly demonstrates that the patients who received the second of a matched pair of donor kidneys with a longer CIT do have a significantly poorer long-term graft survival rates. They also have a higher incidence of DGF and a higher AR rate both of which affect the long-term clinical outcome of the transplanted graft. Thus in our experience, a prolonged CIT does have a negative impact on the long-term kidney graft survival rate. All attempts should be made to minimize the delay for the recipient of the second kidney.

Over the past few years, we have made a number of changes to our protocol, which will enable us to address these issues. Since 1997, the perfusion agent we use at our institution is the University of Wisconsin solution. At present prospective tissue typing is only available during

daytime office hours (0900–1700) but over the next few months we will have a round the clock 24-h service introduced. This will allow prospective donor tissue-typing and subsequent crossmatching to be done, which will allow speedier transplant candidate selection. Over the past 15 years we have seen a progressive decline in the overall mean CIT—from 22.5 h in 1989 to 18 h in 2004. Thus we hope to see ongoing improvements in long-term graft survival rates as we continue to shorten our CIT.

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