Cyclosporine Immunosuppression and Delayed Graft Function in 455 Cadaveric Renal Transplants

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SINCE the nephrotoxic properties of cyclosporine A (CyA) were first described, there has been concern expressed over the use of CyA in nonfunctioning allograft kidneys.[1] Several investigators have reported an increased risk of developing delayed graft function for CyA-treated kidneys when compared with conventionally treated kidneys.[2,3] At the University of Pittsburgh, we have always given CyA preoperatively and have continued the regular dosing protocol postoperatively regardless of graft function.[4,5] The purpose of this study was to review our recent results in terms of delayed graft function and the relationship of CyA to eventual graft outcome.

METHODS AND MATERIALS

A retrospective analysis was performed on 455 consecutive cadaveric renal transplants done at our institution between January 1983 and August 1985. All organs were harvested from heart-beating cadavers and stored in ice slush until transplanted. Local organ procurement, renal transplantions, and postoperative immunosuppressive management were performed under our standard guidelines.[6] Four hundred and thirty-one kidneys were obtained locally; 24 were procured for us by other transplant teams as part of our sharing program, and 190 were obtained from multiple organ donors (Tables 1 and 2).

Delayed graft function (DGF) was defined as the need for dialysis within the first week postoperatively regardless of urinary volume. Permanent nonfunction (PNF) was defined as the failure of the kidney to ever regain enough function to negate the need for continued dialysis.

Other than the type of immunosuppression and graft results, donor factors evaluated included cold storage time, the fate of paired organs, and whether multiple organ recovery was involved. Recipient factors evaluated included age, cause of renal failure, PRA status prior to and at the time of transplant, and primary or retransplant status (Table 2).

Immunosuppression was given preoperatively to all patients and consisted of oral, intravenous (IV), or combined CyA and steroids as previously described.[6] No changes in the standard postoperative CyA dosing were made solely on the basis of DGF. High-performance liquid chromatography (HPLC) whole blood levels were used to aid in dosage adjustment, as was the patients' clinical course.

Statistical analysis of demographic variables was performed using chi square tests. Allograft and patient survival rate were calculated using Kaplan-Meier survival curves.

RESULTS

The incidence of DGF for the study population was 22% (Table 3), which represented 99 kidneys, nine of which were lost early to technical complications. Sixty-two (63%) of the kidneys with DGF eventually regained function adequate to replace maintenance dialysis. Thirty-seven kidneys (8%), however, never regained adequate function and were counted as permanent nonfunctioning losses.

The characteristics of the study population were stratified according to the presence or absence of DGF. As shown in Table 2, the

Table 1. Study Population: Cadaveric Renal Transplants January 1983 Through August 1985

Total transplants (renal)	455
Locally procured kidneys	431
Shared kidneys	24
Ice Storage preservation	455 (100%)

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Table 2. Recipient Demographics (or) Recipient Population Data Base

	Immediate Function	Delayed Graft Function	*P* Value
Diabetic	89/356 (25%)	16/99 (16%)	
Mean age	37.8	38.5	NS
PRA >30 at transplant	49/356 (13.7%)	18/99 (18%)	NS
Multiple organ	145/356 (41%)	45/99 (45%)	NS
Retransplant	48/356 (13.5%)	28/99 (28%)	<0.05
Age >55 yr	34/356 (9.5%)	18/99 (18%)	<0.05

incidence of regrafted patients in the DGF group was 28% *v* 13.5% in the early function group ($P < 0.05$). The other significant difference was in the number of patients older than 55 in the DGF group.

The influence of DGF on graft and patient survival for primary and regrafted recipients is shown in Table 4. The DGF rate for primary transplant recipients was 19%, including eight technical losses, compared with 37% of patients undergoing retransplants ($P < 0.01$). Furthermore, DGF had a significant effect on the long-term graft survival within each group, the effect being most deleterious in retransplant patients where the combination resulted in a 1-year actuarial graft survival of only 32% compared with 62% for primary transplants with DGF. The DGF rate, however, did not have any impact on patient survival which was 96% and 98.6% for retransplants and primary transplants, respectively. The permanent nonfunction rate (Table 5) for the entire group was 8%; however, it was 23.6% for retransplant recipients *v* only 5% for primary transplants ($P < 0.01$). To determine whether the detrimental effect of DGF was related to the length of preservation, we looked at the cold storage for each group was examined. As shown in Table 6, there were no significant differences between any of the groups for either the mean cold storage time or in the percentage of kidneys that were stored for greater than 24 hours.

Table 3. Incidence of Delayed Graft Function on Postoperative Renal Allograft Function

	Number	Percentage
Immediate function	356	78
Delayed graft function*	99	22
Permanent nonfunction†	37	89

*Patients that required hemodialysis within 1 week of transplant.

†Nine permanent nonfuctions were due to technical error.

The fate of paired kidneys was examined to see if donor factors seemed to be more responsible than recipient factors for DGF. There were 69 pairs of kidneys that could be fully evaluated where either one or both kidneys

Table 4. Influence of Delayed Graft Function on Patient Survival

			Actuarial Survival		
			Grafts (%)		Patient
	Grafts	Percentage	1 mo	1 yr	(1 yr; %)
Primary transplants					
Immediate function	308	81	93.5	80	99
Delayed graft function	71	19	72	62	96
Total	379	100	89	77	98.6
Retransplants					
Immediate function	48	63	81	62.5	98
Delayed graft function	28	37	39	32	93
Total	76	100	66	51	96

Table 5. Permanent Nonfunction Rate

	Number of Kidneys	Technical Loss
Primary transplant	19/379 (5%)	8
Retransplant	18/76 (23.6%)	1

had DGF (Table 7). In only 27.5% did both kidneys experience DGF while in 50 pairs, or 72.5%, only one kidney had DGF. In this latter group, there were no significant differences between the ages of the recipients or the storage times for those kidneys that functioned early and those that experienced DGF.

DISCUSSION

The nephrotoxic properties of CyA were first reported in clinical studies by Calne et al,[1] who recommended that the drug be withheld until it was determined that the graft was functioning to avoid the potentially additive effect of a nephrotoxic agent to an already compromised renal unit. Some investigators[2,3] have described a significant increase in DGF to 40% or 50% (Table 8) in patients pretreated with CyA compared with 20% to 30% for patients transplanted with conventional immunosuppression. They have ascribed this difference to CyA nephrotoxicity. However, other reports[7-12] have failed to document any difference in the rate of DGF patients treated pre- or postoperatively with CyA and those treated with conventional immunosuppression including antilymphocyte globulin (ALG). Our overall DGF rate of 22% compares favorably with this latter experience and with our own historical patients treated with conventional immunosuppression,[13] thus supporting the argument that CyA does not increase the rate of DGF.

Furthermore, studies by ourselves[6] and others[14] have failed to show any difference in the incidence of DGF whether CyA is given orally, IV, or in combination preoperatively. Additionally, Belitsky et al[15] showed that there is no difference in the incidence of DGF when high (15 mg/kg) loading doses are used preoperatively *v* low (10 mg/kg) loading doses. However, a significant prolongation of DGF has been demonstrated when IV and oral loading were combined,[6,14] suggesting that the nephrotoxic effect of CyA is less likely to cause DGF than to prolong it if it occurs.

The data from this study also support recent reports on the detrimental effect of delayed graft function on eventual graft survival regardless of whether conventional immunosuppression[16] or CyA is used.[10] It further supports the finding that regrafted patients are more likely to develop DGF with significantly worse results than when primary recipients develop DGF.[12] However, Kramer et al reported that the long-term survival of the kidneys that developed DGF and were treated with CyA was superior in all groups when compared with the DGF long-term survival rates of conventionally treated organs.[10] Our results compare favorably with the CyA results reported by Kramer et al for DGF treated kidneys with the exception of regrafted patients who developed DGF. For this group of patients, the results were the

Table 6. Donor Factor (Mean Cold Ischemia Time)

	Mean ± SD (h)	Stored Over 24 h	
		Number	Percentage
Entire group (455)	25 +/− 7 h	218/455	48
Immediate function (356)	26 +/− 7 h	162/356	45.5
DGF (99)	28 +/− 7 h	56/99	56
Retransplant, DGF (28)	27 +/− 7 h	13/28	46
Retransplant, immediate (48)	25 +/− 7 h	26/148	54

Numbers in parentheses denote the number of patients in each group.

Table 7. Status of Paired Organs

	Pairs		Grafts
	Number	Percentage	With DGF
Pairs with DGF and DGF	19	27.5	38
Pairs with DGF and function	50	72.5	50
Total	69	100	88

Table 8. Rate of Delayed Graft Function With CyA

Institutions	DGF-CyA	DGF-Conventional	*P*
Minnesota*	18.7%	11.5%	n.s.
Oxford*	51%	27%	$p < 0.05$
Birmingham†	34%	40%	n.s.
Brussels*	45%	19%	$p < 0.05$

*Preoperative CyA.

†CyA given after diuresis began.

same as those reported with conventional immunosuppression. Patient survival in all categories was excellent, once again documenting the relative safety of CyA.

We conclude that CyA does not increase the risk of developing DGF and indeed the overall CyA-DGF results are superior to convention-DGF results. Furthermore, we agree with the recommendation of Kramer et al that the probability of DGF should not be a deterrent to the use of CyA in cadaveric transplants.[8]

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