Vasculopathy in the kidney allograft at time of transplantation delays recovery of graft function after deceased-donor kidney transplantation

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Abstract

Objective: The purpose of this study was to evaluate the impact of donor and recipient characteristics on duration of delayed graft function (DGF) and 1-year serum creatinine (SCr), as a surrogate endpoint for allograft survival. **Methods:** We reviewed 120 first cadaver kidney transplants carried out consecutively at our center to examine the effect on 1-year SCr of the presence and duration of DGF. **Results:** DGF rate was 68%, with a median duration of 12 days (range, 1-61). Forty-four (38%) patients presented DGF lasting 12 or more days (prolonged DGF group). Mean donor age was 43 ± 13 years, 37% had hypertension and in 59% the cause of brain death was cardiovascular accident. The mean cold ischemia time was 23 ± 5 hours. Twenty-seven (23%) donors were classified as expanded-criteria donors according to OPTN criteria. The mean recipient age was 51 ± 15 years. The recipients median time in dialysis was 43 months (range, 1-269) and 25% of them had panel reactive antibodies > 0%. Patients with prolonged DGF presented higher 1-year SCr in comparison with patients without DGF (1.7 *vs.* 1.3 mg/dL, respectively, $p = 0.03$). In multivariate logistic regression analysis, the only significant factor contributing to the occurrence of prolonged DGF was the presence of vascular lesions in the kidney allograft at time of transplantation (HR 3.6, 95% CI 1.2-10.2; $p = 0.02$). **Conclusion:** The presence of vasculopathy in the kidney allograft at time of transplantation was identified as an important factor independently associated with prolonged DGF. Prolonged DGF negatively impacts 1-year graft function.

Keywords: delayed graft function; ischemia; kidney transplantation; reperfusion injury.

Introduction

Delayed graft function (DGF) is a common complication in deceased donor kidney transplantation patients, with incidence rates ranging between 5% and 50%. DGF is usually characterized by the need to put patients on dialysis in the first week of after transplantation.[1] The condition's etiology is multifactorial. It stems from ischemic injury occurred before and/or during the procurement of the organ, and is worsened by the reperfusion process. The lack of a consistent definition for DGF, the different practices between care centers, and different donor characteristics account for the variation in incidence rates.[1-3]

DGF rates in Brazil are within the 50%-60% range - well above the values currently found in European and North American centers.[4-6] Delays in graft function recovery result in prolonged hospitalization, increased care costs, and higher risk of nosocomial infection. Additionally, DGF has also been associated with increased risk of acute rejection, reduced glomerular filtration, and worse long-term graft survival.[7,8]

This study aimed to analyze donor and recipient characteristics that have affected the incidence and intensity of DGF, its impact on renal function one year after transplantation - a long term graft outcome marker.[9]

Methods

This retrospective single-center observational study looked into the deceased donor kidney transplants performed in

2010 at the Hospital of the School of Medicine of the University of São Paulo. Five of the 120 transplant patients included in the study were lost within the first week of the procedure, and were thus excluded. DGF was defined as the need for dialysis within the first week of transplantation. Duration of DGF was measured as the number of days until the last dialysis session before the patients were discharged. Using the median duration of DGF as a reference, prolonged DGF was characterized as delayed graft function lasting for periods equal to or greater than 12 days.

Immunosuppression protocols

Maintenance immunosuppression consisted of tacrolimus (Prograft, Astellas Pharmaceuticals, Japan; initial dosage of 0.2 mg/kg/day, with trough levels of 10-15 ng/mL during the first weeks and 5-10 ng/mL onwards), mycophenolate sodium (Myfortic, Novartis Pharma, Basel, Switzerland; dosage of 1.440 mg/day), and corticosteroids. All patients were given a single dose of IV methylprednisolone 500 mg while in immediate preoperative care, followed by 0.5 mg/kg/day of prednisone, with declining doses up to 5-7.5 mg at the end of the second month after transplantation.

Interleukin-2 receptor antagonist basiliximab (Simulect Novartis Pharma) at a dosage of 20 mg on days 0 and 4, or thymoglobulin (Genzyme, Boston, MA) at a dosage of 1-1.5 mg/kg/day adjusted for the peripheral blood CD3 count up to a total of 6-7 mg/kg, were used as induction immunosuppressive drugs. Patients at a higher risk of rejection (PRA > 30%, retransplantation) or with DGF (cold ischemia time > 21h) were given induction thymoglobulin; the introduction of a calcineurin inhibitor was delayed until the day patients were given their last dose of the antilymphocytic drug.

Statistical analysis

Descriptive data were expressed in the form of mean values ± standard deviations and medians (interquartile range or range) for variables with parametric and nonparametric distributions, respectively. Normal distribution was assessed using the Kolmogorov-Smirnov test. The chi-square was used to analyze categorical variables. Student's *t*-test or the Mann-Whitney test were used to compare between two groups. Comparisons between multiple groups were handled by analysis of variance (ANOVA) or the Kruskal-Wallis test.

A multivariate logistic regression model was developed to assess risk factors independently associated with the development of prolonged DGF.

Statistical significance was assigned to events with $p < 0.05$.

Results

Seventy-nine patients (68%) had DGF for a median of 12 days (1-61); forty-four (38%) had prolonged DGF (≥ 12 days). Table 1 shows donor demographic characteristics. Donors had a mean age of 43 ± 13 years, 37% were hypertensive, 4% had diabetes, and 60% died after stroke. Ninety-three percent were on vasoactive drugs, 9% had reversed episodes of cardiac arrest, and 19% stayed in the ICU for more than seven days. The mean serum sodium level was 161 ± 16 mL and the mean daily urine output was 3,455 ± 2,926 mL. The mean cold ischemia time was 23 ± 5 hours. Euro-Collins was the perfusion solution of choice in all cases; 52 (45%) patients had their organs also perfused with the Belzer solution. According to the criteria of the OPTN (Organ Procurement and Transplantation Network), 23% of the donors met the expanded criteria.

Table 1 Kidney donor demographic characteristics

Characteristics	n (%)
Age (years)	43 ± 13
Hypertension	42 (37)
Diabetes	5 (4)
Cause of death	
Stroke	69 (60)
Head trauma	39 (33)
Other	7 (6)
Procurement SCr > 1.5 mg/dL	57 (49)
Reversed cardiac arrest	10 (9)
Prolonged ICU stay (> 7 days)	21 (19)
Use of vasoactive drugs	102 (93)
Serum sodium (mmol/L)	161 ± 16
Daily urine output (mL)	3455 ± 2926
Vasculopathy at procurement biopsy[a]	21 (25)

Data expressed in the form of n (%) or mean ± standard deviation, unless specified otherwise; [a] Data available for 85 patients.

Table 2 shows the demographic characteristics of renal transplant recipients. All patients were given induction immunosuppressive drugs; 46 (40%) were offered an IL-2 receptor antagonist and 69 (60%) were treated with an antilymphocytic drug. This finding is explained by the patient management principles in effect at the service at the time, in which induction thymoglobulin was given to all renal transplant patients with ischemia times exceeding 21 hours. The initial maintenance immunosuppressive regimen consisted of prednisone, tacrolimus, and mycophenolate sodium in all cases. Episodes of acute rejection were recorded in 21 (18%) patients.

Table 2 Kidney recipient demographic characteristics

Characteristics	n (%)
Age (years)	51 ± 15
Time on dialysis (months)[a] (median and range)	43 (1-269)
HLA incompatibility	2.5 ± 1.6
PRA > 0%	30 (26%)

Data expressed in the form of n (%) or mean ± standard deviation, unless specified otherwise; [a] patients on dialysis at the time of transplantation. Five patients (4%) had preemptive transplants.

In order to evaluate the possible differences between patients who had prolonged DGF (recovery time ≥ 12 days) and others, individuals without DGF, subjects with DGF, and patients with prolonged DGF were separated in different groups. No differences were observed between the patients in the three groups in terms of some of the donor-related factors, such as presence of hypertension or diabetes, cause of death, use of vasopressors during donation, reversed cardiac arrest, and serum creatinine at the time of donation. Cold ischemia time, immunosuppressive therapies (induction and maintenance), and episodes of acute rejection were not different between groups. However, as shown in Table 3, the ages of transplant donors and recipients and the length of hospitalization were greater in patients with prolonged DGF. The presence of vascular alterations in donor kidney biopsies at the time of organ procurement was significantly more frequent in patients with prolonged DGF. Vascular changes were assessed qualitatively, and consisted particularly of hyaline arteriolosclerosis and arteriosclerosis.

The analysis of statistically significant variables in the multivariate logistic regression model revealed that among factors donor and recipient age, time on dialysis, cold ischemia time, and vascular alterations in the graft, the presence of vasculopathy in the kidney graft was the only independent risk factor for the development of prolonged DGF [OR 3.6 95% CI (1.2-10.2), $p = 0.02$].

Patients with prolonged DGF had worse renal function one year after transplantation when compared to patients without DGF (prolonged DGF: SCr 1.7 vs. No DGF: 1.3 mg/dL, $p = 0.03$. Figure 1).

Discussion

The study revealed that the presence of vasculopathy in kidney grafts before implantation was an independent risk factor for the development of prolonged DGF, defined herein as the need for dialysis for 12 or more days after transplantation. DGF intensity affected kidney function one year after transplantation, a recognized marker of long-term graft outcome.[9]

Some authors have suggested that DGF does not impact graft survival when not accompanied by acute rejection.[2,10] However, these results are controversial, as data shows that DGF and acute rejection independently affect graft survival in the short and long term and have an additive effect.[7,8] Additionally, some authors have shown that the duration of DGF as a marker of severity negatively affects graft survival.[11,12] Giral *et al*. demonstrated that DGF lasting for more than six days was correlated with decreased graft survival, and that adrenaline administration, cold ischemia times over 16 hours, and recipient age above 55 years were associated with prolonged DGF.[11,13]

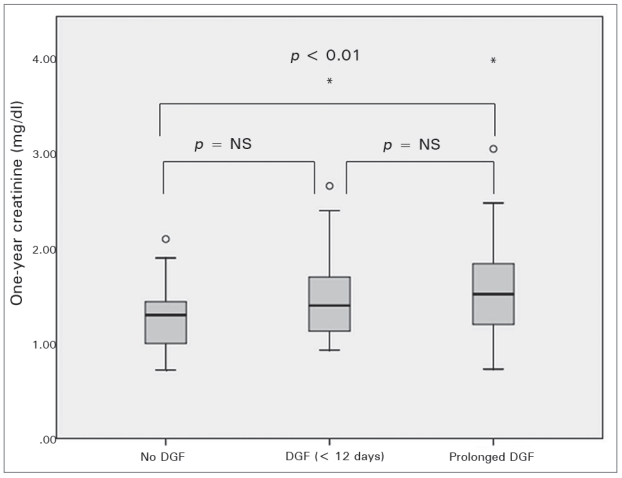
Risk factors for the development of DGF include aspects related to donors, recipients, brain death, and ischemic and reperfusion-related damage.[1,14] The demographic characteristics of multiple organ donors are changing, with increased mean ages and incidences of hypertension and death by stroke. The use of borderline or expanded criteria donors is a global trend to face the severe shortage of organs

Table 3 Baseline characteristics of patients without DGF, with DGF, and with prolonged DGF

Characteristics	No DGF n = 41	DGF (<12 days) n = 35	Prolonged DGF n = 44	*p*
Donor age (years)	38 ± 13	44 ± 12	46 ± 14	0.016
Recipient age (years)	46 ± 15	54± 12	53 ± 16	0.049
Time on dialysis (months)	43 ± 41	58 ± 46	62 ± 51	0.44
Cold ischemia time (h)	23 ± 4	23 ± 6	23 ± 5	0.95
Time of hospitalization (days), median (range)	9 (5-45)	16 (8-77)	31 (13-77)	< 0.0001
Vasculopathy at procurement biopsy	3 (11)	5 (19)	13 (41)	0.02

Data expressed in the form of n (%) or mean ± standard deviation, unless specified otherwise.

Figure 1. Serum creatinine one year after transplantation for patients without DGF, with DGF, and with prolonged DGF.



and the proven superiority of transplants with these donors against dialysis.[15,16] These aspects, along with the intensive care provided to donors before and after brain death, which include the use of vasoactive drugs, cardiopulmonary resuscitation, and prolonged ICU stays, have contributed to the achievement of higher rates of DGF and worse graft survival.[13,17,18] In our case, donors had indirect evidence of volume depletion such as as hypernatremia and polyuria, and approximately half of them had serum creatinine levels above 1.5 mg/dL at the time of organ procurement. Additionally, in all cases the Euro-Collins perfusion solution, known to contribute to increased incidences of DGF, was used for organ preservation.[19]

The presence of vascular lesions in biopsies on time zero has also been associated with a much higher incidence of DGF and worse graft survival.[20,21] Di Paolo et al. looked into 100 consecutive deceased donor renal transplants and found a greater presence of vascular lesions in patients with DGF. Moreover, donor hypertension and DGF were correlated with worse graft survival one year into follow-up in cases of organs with more histological injuries. These results are similar to those found in our study, which showed that certain donor features were determining for the presence and intensity of DGF, with deleterious effects upon graft function one year after transplantation.

The presence of arteriolosclerosis and arteriosclerosis in procurement biopsies, usually correlated with longstanding hypertension and advanced donor age, seemed to be related to susceptibility to ischemia and reperfusion and reduced self-protection and regeneration capabilities against such adverse events, leaving patients more prone to experiencing irreversible sequelae. Experimental models have shown that cell protection mechanisms are activated in response to renal ischemia, including rapid decreases in metabolic activity and the transcription of genes with cytoprotective and regenerative effects. In deceased donor kidneys, the expression of genes that encode graft adaptive response such as heme oxigenasse 1, VEGF, and Bcl2, is diminished when compared to live donor kidneys.[22] Such decreased expression may lead to ineffective adaptation to ischemic insults and impaired graft function in the short and long term.[1]

Conclusion

Severe ischemic and reperfusion injuries, correlated among other things to the critical care provided to deceased donors, may produce irreversible damage to susceptible organs affected by injuries related to age and comorbidities, and affect renal graft function up to one year after transplantation.

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