Delayed Kidney Allograft Function after Simultaneous Pancreas-Kidney Transplantation


ABSTRACT
Background. Simultaneous pancreas-kidney transplantation (SPKT) is one of the treatments for insulin-dependent chronic renal failure patients.

Methods. One-year patient and kidney allograft survival rates of 150 patients undergoing SPKT were subjected to Cox regression and Kaplan-Meier analyses. Uni- and multivariate methods identified risk factors involved in allograft and patient survival.

Results. One-year patient and kidney allograft survival rates were 82% and 80%, respectively. Delayed graft function (DGF) \((P = .001; \text{hazard ratio [HR]} 5.41)\) and acute kidney rejection episodes \((P = .016; \text{HR} 3.36)\) were related to 1 year patient survival as well as intra-abdominal infection (IAI) rates. (IAI). One-year kidney allograft survival was related to DGF \((P = .013; \text{odds ratio [OR]} 3.39)\), acute rejection \((P = .001; \text{OR} 4.74)\), and IAI \((P = .003, \text{OR} 6.29)\). DGF was related to a time on dialysis >27 months \((P = .046; \text{OR} 2.59)\), cold kidney ischemia time >14 hours \((P = .027; \text{OR} 2.94)\), donor age >25 years \((P = .03; \text{OR} 2.82)\), and donor serum sodium concentration >155 mEq/L \((P < .0001; \text{OR} 1.09)\). Female kidney to male recipient in 17% of the cases did not increase the risk of DGF. We observed an important correlation between donor serum sodium and creatinine \((P < .0001)\), which suggested undertreatment of diabetes insipidus secondary to brain death.

Conclusions. DGF, acute rejection, and IAI were the main determinants of survival after SPKT. Improving the care of deceased donors may reduce DGF occurrence.

Insulin-dependent patients with chronic renal failure show greater survival rates after simultaneous pancreas-kidney transplantation (SPKT) than with dialysis treatment. Recent data from the United Network for Organ Sharing (UNOS) and the International Pancreas Registry have shown, that 1-year patient survivals are >95% after SPKT and 1-year kidney allograft survivals ~90%. Patient death with a functioning graft has been reported to cause ~50% of the grafts that subsequently fail. Several risk factors from both recipients and deceased donors associated with delayed kidney allograft function (DGF) may also play important roles after SPKT. However, there are few data regarding patient and kidney allograft survival rates after SPKT at non-USA centers. In addition, identification of those risk factors may contribute to the development of better therapeutic strategies. In the present study, we performed a retrospective analysis of 150 patients undergoing SPKT at our center to assess risk factors for 1-year patient and kidney allograft survivals.

SUBJECTS AND METHODS
Subjects
Between December 2000 and August 2006, we performed 150 SPKT using enteric drainage in 143 patients and bladder drainage in an iliac or caval vein anastomosis was performed in all cases. Belzer and Eurocollins solutions were used for pancreas and kidney preservation, respectively. Only heart-beating donors were selected for organ donation. Age >45 years and family history of diabetes in first-degree relatives were exclusion criteria for dona-
tion. Immunosuppression and postoperative management have been previously described.11

Endpoints
The primary endpoints of the study were 1-year patient and kidney allograft survival rates. Secondary endpoints included assessment of risk factors. In general, we assumed all deaths within the first 90 days after transplantation to be transplant related. DGF was defined as the necessity for dialysis in the first week after transplantation. Intra-abdominal infection (IAI) included peripancreatic abscesses and anastomotic leaks. Our Ethics Committee approved the study.

Statistical Analysis
All results are reported as mean ± SD unless otherwise indicated. Statistical analyses were performed using SPSS 12.0 (Chicago, IL, USA). Fisher exact, t test, and analysis of variance were performed for numeric variables and Pearson χ² test for categoric variables. Correlations were performed using the Cox proportional hazard model. Log-rank analysis and Kaplan-Meier curves evaluated patient and graft survivals, with patient deaths counted as graft losses regardless of the functional status at the time of demise. If the graft was removed before patient death, data were computed as death with a nonfunctioning kidney. All putative factors univariately associated at P ≤ .3 were entered simultaneously into a backward binary logistic regression model with those factors analyzed as the dependent variable. Results were reported as odds ratio (OR) or hazard ratio (HR) and 95% confidence intervals. The statistical analysis assumed significance where P < .05.

RESULTS
Demographic data from recipients and donors are described in Table 1. One-year patient and kidney and pancreas allograft survivals were 82%, 80%, and 76.7%, respectively. Mean time of death was 78.2 ± 82.1 days (range, 3–259 days). Most deaths (70.4%) occurred during the first 90 days after transplantation; 8 patients succumbed thereafter, each case due to infection. Analysis variables obtained from the Cox regression showed that the occurrence of DGF (P < .001; HR, 5.41; 95% CI, 1.98–14.77), acute kidney allograft rejection (P = .016; HR, 3.36; 95% CI, 1.25–9.08), and IAI (P < .0001; HR, 4.15; 95% CI, 1.96–10.36) were the main factors correlated with patient survival during the first year.11 Figure 1 shows patient survivals related to the occurrence of DGF and acute rejection episodes. Risk factors among deceased donors showed no direct influence on 1-year patient survival rates. Although DGF did not increase the risk of acute kidney rejection (P = .81), the patient survivals among cases without DGF and without rejection was 92.6%, whereas those without DGF but with rejection was 77.1%. The 1-year patient survival rates in cases with DGF and without rejection was 69.6% compared with 45.4% when both DGF and rejection were present (log-rank = 13.91; P = .0002). The main cause of recipient death after transplantation was sepsis (66.7%). The most frequent was IAI (55.6%), followed by pulmonary infections (44.4%).11 In addition, hemorrhagic shock (18.5%) and cardiovascular complications (14.8%) contributed to first-year mortality.11 Regarding kidney allograft survival rate, 30 transplants were lost during the first year, and the main cause was death with a functioning renal graft (83.4%), followed by acute rejection (13.3%) and death with a nonfunctioning kidney allograft (3.3%). Logistic regression analysis showed that DGF (P = .013; OR, 3.39; 95% CI, 1.29–8.88), acute rejection (P = .001; OR, 4.74; 95% CI, 1.89–11.92), and IAI (P = .003; OR, 6.29; 95% CI, 1.9–20.8) were also the main risk factors influencing kidney allograft survival during the first year after transplantation.

In an attempt to identify risk factors that contributed to DGF occurrence, a multivariate analysis showed that time on dialysis >27 months (P = .046; OR, 2.59; 95% CI, 1.02–6.8), cold ischemia time >14 hours (P = .027; OR,
DISCUSSION

We analyzed the 1-year patient and kidney survival rates after SPKT at our center. DGF, acute rejection episodes, and IAI showed important impacts on patient and kidney allograft survivals.

Our incidence of delayed renal graft function (22.7%) was greater than that reported by the UNOS database (4%), although the cold ischemia time was similar. This greater number motivated us to identify risk factors for DGF.

The impact of DGF on patient survival may be explained by the effects of immunosuppressive drugs administration in uremic dialyzed patients with augmented risks of infection. Additionally, acute kidney rejection may reinforce the risk of infection owing to corticosteroid pulses and/or antithymocyte therapy.

DGF has been shown to independently predict 1-year and long-term kidney allograft loss, although other authors have suggested influences on renal function but not on kidney survival. In the present study, the main factors associated with DGF were similar to the literature, including time on dialysis, cold ischemia time, and donor age, but not donor serum sodium. First, kidney cold ischemia time among our patients was ~14 hours compared with >24 hours usually described in the literature for isolated renal grafts. We would therefore have expected to observe a lower incidence of DGF, because it has been reported that for every 6 hours of cold ischemia there is a 23% increase in the risk of DGF. Therefore, well known factors involved in DGF development, such as those affecting donor kidney during the diagnosis of brain death and ischemia-reperfusion lesions, may have been more severe in our cases.

Brain death is associated with hypotension secondary to hypovolemia, cardiac dysfunction, and vasodilatation. Providing adequate treatment for these conditions might generate healthier organs for procurement. In Brazilian hospitals, vasopressin is usually not available for patients with brain death owing to its high cost. Therefore, our donors, two-thirds of whom had brain trauma, were not properly treated for diabetes insipidus, one possible explanation for the association between the elevated donor serum sodium and the increased risk of DGF after SPKT, which has been shown to adversely affect short-term out-

Fig 1. (A) One-year patient survival comparing kidney DGF and no DGF. (B) One-year patient survival comparing acute kidney allograft rejection and no acute kidney allograft rejection.

Fig 2. Correlation of donor serum sodium and creatinine.
comes among liver transplantations. In addition, correction of donor hypernatremia may decrease liver graft loss. The mechanisms by which hypernatremia damages hepatocytes and probably renal tubular cells are not clear, but seem to involve ultrastructural particularly mitochondriae changes. Secondly, renal medullary tubular cell are resistant to hyperosmolarity induced by sodium chloride and urea, because they show increased production of heat shock protein 70. In most cases, our deceased donors were not only hypernatremic but also severely hypovolemic under vasoactive drug treatment, which exacerbated the injury inasmuch as the induction of chaperones by hypernatremia is abrogated by severe renal hypoperfusion. In addition, the hyperosmolar Eurocollins preservation solution (340 mOsm), which is rich in intracellular ions to minimize cellular swelling secondary to suppression of Na+/K+ pump by cold storage, may have limited effect on tubular cell integrity. In this way, donor resuscitation was probably one of the main determinants of the DGF occurrence owing to kidney ischemic injury. However, the low number of donors did not allow us to exclude them, but efforts must be made to minimize organ injury in the future. Thus, induction therapy with antithymocyte globulin may be a useful strategy to decrease the risk of DGF by calcineurin inhibitor avoidance and subsequent afferent arteriolar vasoconstriction during the first days after transplantation. However, the increased risk of infection was a matter of concern among our cases.

The second risk factor related to patient and kidney survival was acute kidney rejection episodes, which affect both-short and long-term renal survival after SPKT. UNOS data have shown that long-term kidney graft survival was worse when both pancreas and kidney are involved compared with isolated kidney rejection after SPKT. Our data must be regarded with caution, because in most causes we only biopsied the kidney graft. We did not find an association between acute rejection episodes and DGF, although it has been described in the literature. We did not observe associations between acute rejection episodes and patient sensitization, retransplantation, or ethnicity. Other workers have noted the presence of both acute rejection episodes and DGF to be associated with poorer kidney allograft survival. In addition, kidney DGF may affect not only renal allograft function but also pancreas allograft function. The third risk factor affecting kidney graft function was IAI, which reflected the number of deaths with a functioning graft previously discussed in another study by our group.

In conclusion, DGF, acute rejection episodes, and IAI showed important effects on patient and kidney allograft survival. New strategies should be implemented, including optimization of donor care and minimization of ischemia-reperfusion injury by the use of antithymocyte globulin, University of Wisconsin-Belzer solution for kidney preservation, as well as pulsatile perfusion.

REFERENCES

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