Influence of Surgical Complications on Kidney Graft Survival in Recipients of Simultaneous Pancreas Kidney Transplantation

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ABSTRACT

Purpose. Simultaneous pancreas-kidney transplantation is the gold standard treatment for patients with end-stage renal failure secondary to insulin-dependent diabetes mellitus. This kind of transplantation is a complex operation associated with a high incidence of surgical complications and mortality risk which could influence graft survival. The aim of this study was to establish the influence of different grades of postoperative complications, classified according to Clavien-Dindo, on the rate of kidney graft loss.

Methods. We performed an observational retrospective review of all simultaneous transplantations performed between February 1989 and May 2012. Factors examined were related to recipient and donor characteristics, surgical procedures, and postoperative outcomes. For this purpose, Kaplan-Meier analyses and Cox-Regression tests are used.

Results. One hundred thirty-nine transplantations were performed. Complications grades I, II, and IIIa were experienced in 81 (58.3%) patients, and grades IIIb and IVa-b in 55 (39.6%). Multivariate analysis showed an influence of panel reactive antibody (hazard ratio [HR]: 10.79; $P = .003$), incidence of acute rejection (HR: 2.55; $P = .03$), and complications grouped into grades IIIb and IVa-b (HR: 3.63; $P = .02$). Kaplan Meier analysis showed worse kidney graft survival rate in groups grades IIIb and IVa-b compared to grades I, II, and IIIa (86.6% vs 98.7% at 1 year and 81.8% vs 97.3% at 5 years; $P = .001$).

Conclusions. Despite being the gold standard treatment for these patients, pancreas and kidney transplantations have numerous complications which could influence the prognosis of graft kidney survival.

SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION (SPKT) is the gold standard treatment for patients with end-stage renal failure secondary to insulin-dependent diabetes mellitus [1]. SPKT compared with cadaveric kidney transplantation alone is associated with better long-term patient survival rates [2]; however, SPKT is a complex operation associated with a high incidence of surgical complications and mortality risk [3]. A number of risk factors have been described for patient and graft survival associated with donor, recipient, immunologic, immunosuppressant therapy, and surgical outcome [3–5]. Several investigators have described the negative influence with postoperative complications in SPKT forecast, although most of them focus on pancreas graft prognosis, with which the majority of complications are associated [6]. There is little and controversial literature about the influence of these complications in graft kidney medium and long-term prognosis [7,8].

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Table 1. Description and Comparison of Clinical Variables Depends on the Severity of Grade of Complication Grouped in Clavien Grades I (n = 48); II (n = 25); IIIa (n = 9) Compared to Clavien Grades IIIb (n = 41); IV (n = 13); V (n = 3)

Variable μ ± SD; N (%)	Clavien I; II; IIIa (n = 82)	Clavien IIIb; IVa-b; V (n = 57)	*P* Value	Total
Receptor variable				
Gender male	61 (75.3)	45 (77.6)	.76	106 (76)
Age (y)	37.85 ± 6.63	39.16 ± 7.98	.18	38.50 ± 7.24
HTA (yes)	27 (33.3)	19 (32.8)	.94	46 (33.1)
BMI (kg/m^2)	23.17 ± 2.92	23.26 ± 2.75	.85	23.1 ± 2.84
Diabetes (mo)	292.43 ± 73.51	298.53 ± 77.38	.63	294.98 ± 74.3
Dialysis				
Predialysis	7 (8.6)	5 (8.6)	1	12 (8.6)
Dialysis (mo)	18.33 ± 18.60	20.19 ± 22.86	.58	19.11 ± 20.43
Peritoneal dialysis*	15 (20.3)	13 (24.5)	.57	28 (22)
Transplantation variables				
Cold ischemia (hours)	12.10 ± 3.25	13.49 ± 3.17	.01	12.68 ± 3.28
Enteric derivation	71 (87.7)	46 (79.3)	.18	117 (84.2)
Days to discharge	26.73 ± 19.51	50.86 ± 31.23	.00	36.80 ± 27.68
Immunological variables				
Immunosuppression†	58 (74.4)	32 (60.4)	.09	90 (68.7)
HLA incompatibilities	4.65 ± 1.00	4.89 ± 1.28	.33	4.75 ± 1.12
PRA (<10%)	75 (92.6)	52 (89.7)	.54	127 (91.4)
N°Rejections/patient	0.17 ± 0.44	0.21 ± 0.40	.64	0.19 ± 0.43
DGF (yes)‡	8 (9.9)	19 (32.8)	.00	27 (19.4)
Donor variables				
Gender male	55 (67.9)	38 (65.5)	.79	93 (66.9)
Age (years)	26.19 ± 9.30	26.96 ± 9.88	.63	26.51 ± 9.52
BMI (kg/m^2)	23.53 ± 2.47	23.74 ± 2.41	.64	23.61 ± 2.44
ICU (days)	2.91 ± 2.82	3.09 ± 4.48	.80	2.98 ± 3.55
Creatinine (mg/dl)	0.85 ± 0.29	0.85 ± 0.35	.80	0.85 ± 0.31
Inotropic Drugs (yes)§	56 (69.1)	44 (75.8)	.40	100 (71.9)
Cause of death (TCE)	46 (56.7)	29 (50.0)	.50	75 (53.9)

Abbreviations: BMI, body mass index; PRA, panel reactive antibodies; DGF, delayed graft function (dialysis in the first week after transplantation); ICU, intensive care unit; HTA, hypertension; TCE, Head trauma.
*Among the patients in dialysis (n = 127).
†Basiliximab + tacrolimus-based immunosuppression (9 dates missing).
‡Dialysis in the first week after transplantation.
§Drugs with α-adrenergic effect.

Other problems exist in the variability and subjectivity of the selection of the nomenclature of such complications, making it very difficult to standardize and compare series. In 1992, Clavien and Dindo [9] presented a novel approach to rank complications by severity based on the therapy used to treat them. This system was revisited in 2004, and the authors developed a new five-scale classification system with the aim of presenting an objective and reproducible way of reporting negative events after surgery. Recently this classification has been evaluated providing strong evidence that this method is valid and applicable in many fields of surgery, including urology and solid organ transplantation [10,11]. The aim of our study was to establish the influence of different grades of post-operative complications, classified according to Clavien-Dindo, on the rate of kidney graft loss.

METHODS

An observational retrospective study was performed of all SPKT in type I diabetes patients performed at the Reina Sofia University Hospital between February 1989 and May 2012. Data from paper and electronic medical records were incorporated to an assembled transplantation database complying with Spanish law regulating the confidentiality and protection of clinical data.

Patient demographics, donor characteristics, immunosuppressant therapy, immune parameters, and surgical details were recorded. All patients were reviewed in our center until death or the date of last follow-up examination.

Surgical complication was defined as any deviation from the normal postoperative course with the need for pharmacological or invasive treatment. Intra-abdominal infection (IAI) was diagnosed on the basis of clinical symptoms (fever); analytical (leukocytosis and increased serum C-reactive protein level); microbiological examination of blood, pus, or drained liquid; and abdominal collection imaging with computed tomography.

Pancreas graft failure was defined as the permanent requirement for exogenous insulin after transplantation, and kidney graft failure was defined as the permanent requirement for dialysis after transplantation, or in the case of a pre-dialysis patient, a return to their pretransplantation renal function.

The severity of complications was classified according to the modified Clavien-Dindo classification, recording only the most severe complication when patients developed others; grade I, no complication; grade II, drug therapy; grade IIIa, invasive intervention without general anesthesia; grade IIIb, invasive intervention requiring general anesthesia; grade IVa, life-threatening

complication with single-organ dysfunction, including patients with graft failure; grade IVb, life-threatening complication with multi-organ dysfunction; and grade V, death.

Surgical Technique and Immunosuppression

The procedure was performed through a midline incision. First, the pancreas-duodenal graft was placed in the right iliac fossa, with the vein and artery anastomosed to the cava and the common iliac artery. Bladder drainage was performed from 1989 to 2000, and since 2001 enteric drainage was performed in all patients.

Secondly, with the same midline incision, the kidney allograft was placed in the left iliac fossa, using an intraperitoneal approach, with a termino-lateral anastomosis for the graft vessel to the external iliac vessel and a Lich–Gregoire procedure for ureteral anastomosis.

Most SPKT patients received quadruple sequential therapy. Induction therapy included antilymphocyte monoclonal antibody antithymocyte globulin or OKT3 up to 1999, and with the anti–interleukin-2 receptor monoclonal antibody (basiliximab) thereafter. Maintenance therapy comprised of corticoids, a calcineurin inhibitor (cyclosporine and, from 1999 onward, tacrolimus) and a purine synthesis or DNA inhibitor (azathioprine and, from 1999 onward, mofetil/mycophenolate sodium).

Statistical Analysis

Kidney graft survival was censored for patient death with a functioning graft, and patients with no record of death or graft failure were censored at the date of last follow-up examination.

Clinical variables are described and compared between both groups using Student t and χ^2 tests. A Kaplan-Meier method and log-rank test were used to determine survival probabilities at various times post-transplantation. Cox proportional hazard models were used in univariate and multivariate analyses to assess the influence of surgical complications, adjusted for other potential influential variables, on long-term graft survival. For the regression analysis and Kaplan-Meier, the variable of postoperative complications was divided into two groups: grade I/II/IIIa ($G \leq$ IIIa) versus grade IIIb/IVa-b ($G \geq$ IIIb). Death was censored (grade V).

The SPSS version 17.0 (SPSS Inc., Chicago, Ill) was used to analyze the data and a P value of less than .05 was deemed to be significant.

RESULTS

We examined 139 SPKT cases. The median recipient age was 38.5 ± 7.24 SD years. Average follow-up time was 85.41 ± 63.84 SD months. Table 1 shows the patient, donor, and surgical details comparing two groups.

Multivariate Cox regression (proportional hazard analysis) revealed a statistically significant influence in the rate of kidney graft loss in an independent manner for high panel reactive antibody levels (hazard ratio [HR]: 10.79, 95% confidence interval [CI]: 2.25–51.68; $P = .003$), incidence of acute rejection (HR: 2.55, 95% CI: 1.07–6.08; $P = .03$), and the group $G \geq$ IIIb of postoperative complications (HR: 3.63, 95% CI: 1.22–10.89; $P = .02$; Table 2).

One or more complications occurred in 91 (65.5%) SPK transplant recipients. IAI was the most frequent cause of therapy needed to correct the complication in 46 of 91 complications (50.5%). Most of them were managed successfully with antibiotic therapy alone: 17 of 46 (36.9%) "grade II," or plus percutaneous drainage in 7 of 46 (15.2%) "grade IIIa." However, IAI was the most severe complication after SPKT, with a high rate of re-laparotomy in 15 of 46 (32.6%) "grade IIIb," with pancreas loss in 2 of 46 (4.4%) "grade Iva," severe systemic infection in 2 of 46 (4.4%) "grade IVb," and 3 of 46 (6.5%) deaths "grade V." The most commons urological surgical complications were hematuria in 4 cases (3 related to bladder derivation). The main cause of postoperative kidney and pancreas loss was graft thrombosis in 7 recipients (4 pancreas and 3 kidneys, "grade IVa").

Table 2. Results of Univariate and Multivariate Cox Regression

	Univariate			Multivariate		
	HR	P	95% CI (HR)	HR	P	95% CI (HR)
Clavien G ≤ IIIa vs. G ≥ IIIb	3.06	.02	1.14–8.18	3.63	.02	1.22–10.89
PRA (<10%–>50%)	13.07	.00	3.62–47.29	10.79	.00	2.25–51.68
DGF (yes)	3.72	.00	1.54–9.01		NS	
Rejections (number)	3.53	.00	1.71–7.32	2.55	.03	1.07–6.08

Patient death was censored as a cause of graft loss.
Likelihood ratio test = 24.14.
$P = .00$.
GL = 4.
Univariate analyses in all patients in multivariate analysis patients with Clavien V were censored.
Abbreviations: HR, hazard ratio; CI, confidence interval; PRA, panel reactive antibodies; DGF, delayed graft function; GL, degrees of freedom.

Survival Analysis

Kidney graft survival rates at 1 and 5 years were 92.6% [95% CI: 88–97] and 89.8% [95% CI: 85–95], respectively. This survival rate was significantly lower in $G \geq$ IIIb compared to $G \leq$ IIIa. ($G \geq$ IIIb 1- and 5-year kidney survival was 86.6% [95% CI: 77–96] and 81.8% [95% CI: 71–93], respectively, and $G \leq$ IIIa was 98.7% [95% CI: 96–100] and 97.3% [95% CI: 94–100], respectively, $P = .001$; Fig 1). Patients, graft kidneys, and pancreas survival functions at 1 and 5 years were 94.1% and 91% for patients, 92.4% and 90.2% for kidneys, and 90.8% and 84.5% for pancreas, respectively.

DISCUSSION

SPKT is the gold-standard treatment for patients with type I diabetes and chronic kidney failure. Numerous complications have been reported in the literature, which could influence the prognosis of the graft pancreas survival, but there is less literature reporting their influence on kidney survival. The main finding of this study was that SPKT patients with surgical complications grades IIIb and IVa-b, evaluated by the Clavien-Dindo method, showed worse kidney graft survival rates than patients with grades I, II, and IIIa, and represent an independent factor in the rate of kidney graft loss.

SPKT is reputed to carry the highest risk of surgical complications of all routinely transplanted solid organs up to 43% [12]. Most published articles focus on complications that require reoperation but do not use available reporting systems [8,13,14], which will allow series comparison and

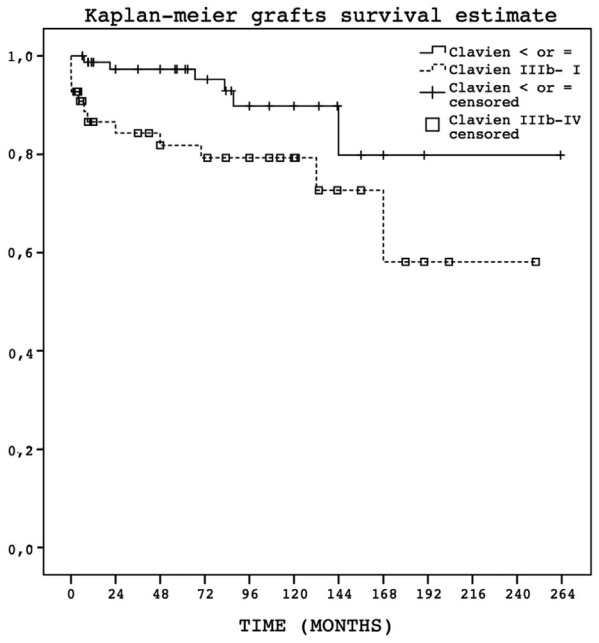

Fig 1. Relationship between kidney graft survival and postoperative complications classified according to Clavien (divided into two groups; G $\leq$ IIIa vs G $\geq$ IIIb/IVa-b) (test long-rank: 5.54; $P = .02$).

conclusions to be reached to avoid complications and improve patient care. To address this need, there has been an increase in the number of studies using the Clavien-Dindo system [15–17]. Recently the European Association of Urology recommended this grading system to report complications [18]. These studies report re-laparotomy rates ranging from 10% to 65%, most of them related to pancreas graft (up to 60% to 70%) [13,14,19]. Our results included 57 of 139 (41%) re-operations, most of them without graft loss or death (41/57 [72%]). Pancreas grafts were the main cause of re-intervention in 39 of 57 (68.4%) patients.

These complications and subsequent graft damage can have profound effects on patient outcome. Previous studies have shown that SPKT recipients with early technical failure of the pancreas have significantly inferior kidney graft survival rates compared to those who did not (59.5% vs 82% at three years, $P < .001$) [7]. Contrary to this, Banga [8] reveals that long-term kidney survival remains unaffected in patients who experience early re-laparotomy compared to those who did not (82% versus 83%, at 5 years $P = .412$). In our study, the survival rate of kidney grafts was lower among patients who presented with grades IIIb or IVa-b complications than those who did not have early technical failure (kidney survival rate at 5 years 81.8% vs 97.3%; $P = .02$), showing an independent influence adjusted for immunologic and other important variables that influence postoperative complications.

This data shows that complications have serious effects on post-transplantation recovery and long-term graft survival. Two different mechanisms could contribute to kidney loss in situations of severe systemic infection; first, patients suffer significant periods of hemodynamic instability and require inotropic drugs, factors contributing to delayed graft function or thrombosis; second, an increased incidence of acute rejection because of the temporarily reduced or discontinued immunosuppression that is often necessary in cases of infections. Therefore, in this group, reduced kidney survival could be directly or indirectly attributed to surgical complications.

Despite the complications, long-term graft and patient survival rates of our cohort are similar to others. With regard to long-term outcome, 5-year patient, kidney, and pancreas survival rates in our center were 92%, 89%, and 80%, respectively. Sutherland [20] reported 4-year patient, kidney, and pancreas survival rates of 88%, 81%, and 82% (74% if enteric drained), respectively. Sollinger [13] reported 5-year patient, kidney, and pancreas survival rates of 89%, 80%, and 76%, respectively.

The present study has certain limitations. As with all observational retrospective studies, our results should be interpreted carefully because of the possibilities of bias. More studies with larger cohorts and longer follow-up times are required to confirm and compare with these results.

CONCLUSIONS

SPKT is associated with high postoperative morbidity and with a high re-operation rate that leads to increased graft loss in this early period. The presence of different grades of complications produces a decrease in kidney graft survival probably related to the mechanisms of complications. However, the positive results obtained reinforce SPKT as the gold-standard treatment in type I diabetes patients with renal failure.

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