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Early morbidity after pancreas transplantation

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Summary

This study aims to evaluate and compare the early outcome of both pancreas-alone transplantation (PTA) and simultaneous kidney–pancreas transplantation (SPKT) focusing on the complications affecting the first month after the procedures. The records of all patients who underwent PTA or SPKT were reviewed. We considered the length of ICU stay, the need for postoperative ventilatory support, hemodynamic and metabolic data (arterial pH, serum glucose, need for exogenous insulin), infectious diseases incidence, microbiological colonization rate and any kind of postoperative complication arising during the first month after the transplantation. PTA recipients underwent a quicker surgery ($P < 0.01$) with shorter ICU stay ($P < 0.05$) and a lower need for postoperative mechanical ventilation ($P < 0.05$). They also had a higher hemodynamic stability ($P < 0.05$) with less cardiological complications ($P < 0.05$) in the intra- and postoperative phases; bacterial colonisation was also less frequent in PTA recipients ($P < 0.05$). On the contrary, no significant difference was noted with regard to postoperative nausea/vomiting, sudden myocardial death, ICU re-admissions, graft function, rate of rejection, grafts explantation and re-transplantation. PTA could be considered as preemptive for severe diabetic complications in patients with long-lasting severe type I diabetes. However, establishing the correct timing of PTA is of paramount importance in order not to expose the patients early to risks arising from a major surgery and heavy immunosuppressive treatments.

Introduction

Pancreas transplantation is a valid therapeutic option for improving the quality of life of patients affected by severe type I diabetes as it can reduce the disease-related long-term complications. This is because, after the transplant procedure, the glycemic balance is restored and the progression of diabetes-induced physiopathological alterations involving different organs and functions are slowed down (as it also happens for the appearance of new diabetes-related complications) [1].

Two types of pancreas transplantations are most frequently performed at our center: pancreas alone transplantation (PTA) and simultaneous kidney–pancreas transplantation (SPKT); in the latter, kidneys may be obtained from a cadaveric (SPKT) or a living donor (SPLKT).

Ideal candidates for PTA are subjects with unsatisfactorily controlled glycemia levels, hypoglycemic episodes, good renal function (creatinine clearance >80 ml/min, proteinuria <3 g/24 h), and the simultaneous presence of at least two early diabetes-related complications such as neuropathy, retinopathy or vascular disease [2]. Patients in whom SPKT is indicated are those whose diabetes has led to severe kidney damage leading to cause chronic renal insufficiency, regardless of whether they are treated conservatively (creatinine clearance <30 ml/min) or by means of dialysis.

Medium and long-term survival considerably increased in the last years particularly for PTA patients [3] whereas immunological graft-loss rate remains significantly lower for SPK than for solitary transplant due to the fact that the clinical manifestations of rejection is usually seen first in the renal rather then pancreatic graft (sentinel kidney phenomenon). Therefore, an initial kidney dysfunction may be interpreted as a possible dysfunction also of the transplanted pancreas [1,4].

Given the lack of specific data and reports on the subject, study we aimed to evaluate and compare the early outcome of SPKT and PTA patients focusing on the complications during the first month after the transplant procedure.

Materials and methods

Based on a review of the ICU records, we compared the postoperative course of all of the patients who underwent PTA or SPKT at our Centre between January 1999 and December 2003. We did not consider sequential pancreas after kidney transplantations as, in this period, only five were performed.

At our Institution patients who underwent PTA or SPKT are admitted to the intensive care unit (ICU) where they receive a continuous invasive cardiovascular (central venous and arterial pressures), respiratory, renal and metabolic monitoring or support as needed. All patients were administered i.v. gabexate mesilate, a synthetic protease inhibitor, 1000 mg/24 h and somatostatin 6 mg/24 h to modulate amylase and lipase secretion in the pancreatic graft. Other medications included tramadol 300 mg/24 h in an i.v. continuous infusion to control postoperative pain, s.c. calcic heparin 2000 IU/three times daily for thromboembolic prophylaxis, oral acetylsalicylic acid 100 mg/day when platelet levels exceeded 250 000/mm^3. From 2003, PTA patients underwent systemic heparinization followed by dicumarol therapy [5]. Immunosuppression consisted of 0.8 mg/kg/day i.v. methylprednisolone (Solu-Medrol; Pharmacia, Puurs, Belgium) and then tapered, oral mycophenolate mofetil 2 g/day (Cell Cept; Roche, Wlvwyn Garden city, UK), i.v. Basiliximab 20 mg (Simulet; Novartis, Horsham, UK) on the day of surgery and the fourth postoperative day, and oral tracrolimus (8 mg/dl; Prograf; Fujisawa, Milan, Italy) or cyclosporine (150 mg/dl; Neoral, Novartis, Origgio, Italy) so as to maintain serum concentrations. In patients at high immunologic risks (re-transplant, blood transfusions) and/or panel reactive antibodies (PNA) >10%, the immunosuppressive therapy consisted of 3 mg/Kg/die rabbit anti-human thymocyte ATG immunoglobulins (Thymoglobuline, Sangstat, Cambridge, UK). During the first 3 days after transplantation an anti-bacterial prophylaxis consisting of i.v. 3 g/day second-generation cephalosporin was used. Simultaneously, anti-mycotic and anti-CMV (in case of seronegative subjects receiving grafts from seropositive donors) treatments were started and continued for the first 2 weeks: the former consisting of 400 mg/day fluconazole (Diflucan; Pfizer, Latina, Italy) and the latter of 5 mg/kg ganciclovir (Cymevene; Recordati, Milan, Italy) . Patients were discharged from ICU based on the Troopman's criteria [6].

Our analysis considered the duration of ICU stay, the need for postoperative ventilatory support, hemodynamic and metabolic (pH, glycemia, need for insulin) data, the incidence of sepsis and/or microbiological colonization and the incidence of any kind of postoperative complication arising during the first post-transplant month that required re-admission to our ICU.

The data were statistically analyzed using Student's t-test and the chi-squared test according to Brandt–Snedecor as appropriate (Prism software ver. 2.0; Graph Pad Inc, College Station, TX, USA); $P < 0.05$ were considered statistically significant.

Results

During the study period, 36 patients underwent PTA and 63 SPKT (Table 1). The two groups did not differ with regard to their age. This was probably because SPKT recipients were, in a great number, transplanted early, when the dialytic treatment was started since a little time or at all. At the moment of surgery, 30 SPKT recipients were on dialysis for more than 6 months, the other six since less than 6 months and the remaining 27 never underwent any treatment.

In the SPKT group, 22 bladder drainages, six systemic–enteric drainages and 35 portal–enteric drainages were performed, while in PTA group all but one of the patients received a portal–enteric drainage. The intraoperative phase of the SPKT group was longer and more complex with more frequent episodes of hemodynamic instability (18 SPKT: 17% vs. 2 PTA: 5.5%; $P < 0.05$), respiratory

Table 1. Patients data.

	SPKT	PTA	*P*-value
Patients (number)	63	36	
Age, [years (mean ± SD)]	38.4 ± 6.0	38.6 ± 3.9	0.9
Gender (F/M)	27/36	19/17	0.3
Patients survival at 90 days [n (%)]	59 (94.2)	36 (100)	0.3
Pancreas-graft survival at 90 days [n (%)]	58 (92.8)	34 (92.8)	0.8
Kidney–graft survival at 90 days [n (%)]	58 (92.8)	–	

F, female; M, male; ICU, intensive care unit; SPKT, simultaneous pancreas–kidney transplantation; PTA, pancreas alone transplantation.

(7 SPKT: 11.1% vs. 0 PTA: 0%; $P < 0.05$) and cardiological problems (10 SPKT: 15.8% vs. 1 PTA: 2.8%; $P < 0.05$) (Table 2).

The PTA patients as against the SPKT recipients spent less time in the ICU (3.2 ± 1.2 days vs. 4.7 ± 3.8 days; $P < 0.05$), required less postoperative mechanical ventilation (0 PTA: 0% vs. 7 SPKT: 8.9%; $P < 0.05$), had a lower incidence of arterial hypertension requiring continuous drug treatment (4 PTA: 11.1% vs. 30 SPKT: 47.6%; $P < 0.01$), experienced fewer cardiological complications such as rhythm disturbances or episodes and/or radiological signs of acute pulmonary edema (2 PTA: 5.5% vs. 20 SPKT: 31.7%; $P < 0.01$), and showed less colonization by pathogenic agents (0 PTA: 0% vs. 11 SPKT: 17.4%; $P < 0.01$). With regard to the hemodynamic parameters, the SPKT patients had significantly lower central venous pressure (CVP) values on the first postoperative day ($P < 0.05$) and significantly higher values on the third postoperative day ($P < 0.05$) (Table 3). There were no differences between the PTA and SPKT groups in terms of the clinical consequences of diabetic neuropathy [7] such as the incidence of postoperative nausea/vomiting (11 PTA: 30.5% vs. 16 SPKT: 25.4%), sudden myocardial death with functioning graft as defined by Page and Watkins [8], (0 PTA: 0% vs. 3 SPKT: 4.7%), need for vasoactive drugs (0 PTA: 0% vs. 3 SPKT: 4.7%; $P = 0.3$) and insulin during the postoperative period ($P = 0.2$), or variations in pH ($P = 0.4$). Finally, no difference in the rate of ICU re-admissions was seen (3 PTA: 8.3% vs. 7 SPKT: 11.1%; $P = 0.2$). Similarly, no difference was found in the number of re-transplants of one of the two grafts (2 PTA: 5.5% vs. 0 SPKT: 0%; $P = 0.06$), rate of rejection (6 PTA: 16.6% vs. 17 SPKT: 27%; $P = 0.5$), the rate of grafts thrombosis (2 SPKT: 3.1% and 2 PTA: 5.5% recipients; $P = 0.5$) and the need for grafts explantation (3 PTA: 8.3% vs. 1 SPKT: 1.6%; $P = 0.1$).

Table 2. Intraoperative data.

	SPKT	PTA	*P*-value
Surgery length, [min (mean ± SD)]	525.3 ± 115.5	428.1 ± 79.5	0.0001
Immediate extubation, [n (%)]	56 (91.1)	36 (100)	0.038
Respiratory problems, [n (%)]	7 (11.1)	0 (0)	0.04
Cardiological problems, [n (%)]	10 (15.8)	1 (2.8)	0.04
Hemodinamic Instability, [n (%)]	18 (17)	2 (5.5)	0.006

SPKT, simultaneous pancreas–kidney transplantation; PTA, pancreas alone transplantation.

Table 3. Postoperative data.

	SPKT	PTA	*P*-value
Days in ICU	4.7 ± 3.8	3.2 ± 1.2	0.02
MAP (mmHg)			
POD 1	109 ± 16.1	104 ± 10.9	0.2
POD 2	112.3 ± 12.2	108 ± 10.7	0.2
POD 3	113.5 ± 15.8	108.2 ± 7.9	0.3
CVP (mmHg)			
POD 1	7.2 ± 2.8	8.6 ± 1.9	0.017
POD 2	7.6 ± 2.5	8.4 ± 1.9	0.2
POD 3	7.2 ± 2.1	8.9 ± 2.1	0.023
PH (IU)			
POD 1	7.23 ± 0.1	7.38 ± 0.3	0.4
POD 2	7.38 ± 0.9	7.39 ± 0.0	0.5
POD 3	7.41 ± 0.5	7.41 ± 0.4	0.3
White cell count			
POD 1	14.700 ± 6.700	13.900 ± 4.700	0.4
POD 2	14.700 ± 5.400	15.300 ± 4.900	0.4
POD 3	14.800 ± 8.8	12.900 ± 1.2	0.3
Glycaemia (mg/dl)			
POD 1	124.6 ± 4.1	125.3 ± 5.6	0.9
POD 2	135.9 ± 3.6	128.0 ± 4.5	0.2
POD 3	134.8 ± 5.5	127.7 ± 7.7	0.5

Values are given as mean ± SD.
IU, international units; ICU, intensive care unit; MAP, mean arterial pressure; CVP, central venous pressure; SPKT, simultaneous pancreas kidney transplantation; PTA, pancreas transplantation alone; POD, postoperative day.

Discussion

Type I diabetes causes the impairment of different organs and functions leading to considerable increase in morbidity and mortality mostly as a consequence of severe cerebral and coronary vascular disease [9]. As pancreas transplantation re-establishes normoglycemia, it is believed that such a procedure can prevent or slow the progression of such complications [10].

Our results show that PTA recipients experienced fewer early postoperative complications than those undergoing SPKT. This can be essentially related to the more severe preoperative condition of SPKT patients who, in addition to severe diabetes, are dangerously jeopardized by chronic renal failure [11]. As a consequence, in our series SPKT recipients drugs needed more frequently to treat arterial hypertension (30 SPKT vs. 4 PTA) which, besides being reported to be associated with chronic renal insufficiency, also plays a major role in increasing cardiac risk in patients [12]. In fact, the incidence of both silent and clinically overt cardiac ischemia is higher when diabetes is associated with a renal disease requiring replacement therapy [13]. Moreover, the risk of infection (expressed as the degree of colonization by pathogenic agents) was also higher in the SPKT subjects; this finding may be explained by a reduced immunocompetence because of the superimposition of diabetes and renal insufficiency [10]. Finally, the greater severity of the SPKT recipients'

preoperative conditions also affected their intraoperative course which showed a higher incidence of complications in terms of cardiological accidents, hemodynamic and respiratory instability. On the other hand, the graft's function was not affected by the severity of diabetes. In fact, SPKT and APT patients did not show any difference in the need for exogenous insulin to keep glycemia into normal levels both in the medium and long term (this is considered a front-line marker for the pancreas graft function) [14]. Moreover, the re-transplantation rate was the same in the two groups of recipients. The fact that the two groups of patients did not differ in terms of their age is probably due to the fact that the SPKT recipients underwent the transplant procedure far before the occurrence of an irreversible renal damage or after having started the dialytic treatment only since few months.

Another discrepancy pointed out by our data, although not statistically significant, between SPKT and PTA recipients is their different coagulation profile highlighted by their graft thrombosis rate which was 2.9% and 5.4% respectively ($P = 0.5$). This discrepency may be explained by the fact that uremic-related coagulopathy may protect SPKT patients against the risk of pancreatic graft (a low-flow organ) thrombosis [11]. Again, the different degree of the preoperative diabetes severity significantly affects the outcome of such a class of patients with the PTA patients showing a more favorable postoperative course from this point of view [15].

With regard to the immunosuppressive and surgery-related postoperative complications, our data are consistent with what was already reported [13] (both seem to comparably affect the two groups of patients during the first 90 days after the transplant). Nevertheless, a difference is reported after the first 3 months from the procedure [16]. In any case, grafts and recipients survival rate seem to have become gradually similar in the two groups over time [15] where, in the long-term, complications related to the diabetic neuropathy and the microvascular alterations induced in the native kidney begin to decrease 5 years after the transplantation and the morbidity and mortality from cerebrocardiovascular accidents remain high during the first post-transplant years [14].

Conclusions

As PTA leads to fewer early postoperative adverse events, it could be considered as preemptive for the severe complications related to long-term diabetes. However, establishing the correct timing of PTA is of paramount importance in order not to expose patients too much early to all of the risks arising from a major surgery and immunosuppressive treatments as it has been shown that PTA recipients are at great risk for graft rejection and thrombosis than SPKT patients and only heavy immunosuppression regimens and sophisticated surgical techniques are nowadays capable of improving the results related to solitary pancreas transplantation [17]. Therefore, PTA procedures should be performed only at very experienced centres.

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