Effect of Pretransplant Dialysis Modality on Outcomes After Simultaneous Pancreas-Kidney Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 **Juulia Räihä**
ABCDEG 1 **Ilkka Helanterä**
BE 2 **Agneta Ekstrand**
B 1 **Arno Nordin**
ABD 1 **Ville Sallinen**
ABCDEG 1 **Marko Lempinen**

1 Department of Transplantation and Liver Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
2 Department of Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Corresponding Author: Juulia Räihä, e-mail: juulia.raiha@hus.fi
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Background: Pretransplant dialysis modality may affect outcome after simultaneous pancreas-kidney transplantation (SPKT), and it has been suspected that peritoneal dialysis (PD) is associated with more postoperative complications compared to hemodialysis (HD). The aim of this study was to evaluate whether pretransplant dialysis modality affects the risk for postoperative complications in SPKT recipients.

Material/Methods: This was a retrospective longitudinal cohort study of all patients undergoing SPKT from 2010 to 2017, during which 99 simultaneous pancreas-kidney transplantations were performed. Three pre-emptive transplantations were excluded. Patient groups receiving PD (n=59) or HD (n=37) were similar regarding baseline characteristics. All complications occurring during the first 3 months after transplantation, as well as patient and graft survival, were analyzed.

Results: There were no significant differences in postoperative complications between groups, with similar rates of intra-abdominal infections (8% in HD *vs.* 10% in PD), pancreatitis (16% in HD *vs.* 17% in PD), gastrointestinal bleedings (22% in HD *vs.* 10% in PD), and relaparotomies (27% in HD *vs.* 24% in PD). None of the patients had venous graft thrombosis. Past peritonitis was not associated with increased risk for postoperative complications in PD patients. Patient and graft survival were similar between PD and HD groups.

Conclusions: Peritoneal dialysis is not a risk factor for postoperative complications after SPKT.

MeSH Keywords: Kidney Transplantation • Pancreas Transplantation • Patient Outcome Assessment • Peritoneal Dialysis • Postoperative Complications • Renal Dialysis

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Background

Simultaneous pancreas-kidney transplantation (SPKT) has established its position in treating patients with type 1 diabetes and end-stage renal disease [1–4]. It improves the prognosis [4–6] and quality of life [3,7] compared to kidney transplant alone (KTA). The restored glycemic control improves renal graft outcome in the long-term and can reduce secondary complications of type 1 diabetes [2,3]. However, surgical complications related to SPKT are common [8], even though there has been a significant decrease due to better identification of risk factors, improved surgical techniques, and better prophylaxis and immunosuppressive regimens [4,9]. Despite improved results in outcome and complications, the number of all pancreas transplantations has decreased steadily from the beginning of the 21st century until only just recently, taking a slight turn in SPKT and pancreas transplantation alone (PTA) [10]. The field of islet transplantation and artificial pancreas is evolving, and with that, the overall trend of pancreas transplantations, especially PTA and pancreas after kidney (PAK) transplantations, may continue to decline in the future [2]. For now, the improving results of pancreas transplantations encourage centers to allow more patients onto waiting lists, as there are still many barriers to overcome before islet transplantation and artificial pancreas use will replace this method.

It is unclear whether pretransplant dialysis modality affects outcome. There are several studies comparing hemodialysis (HD) and peritoneal dialysis (PD) in patients receiving KTA [11–16], but few have focused on SPKT. It has been suspected that PD is associated with more surgical complications compared to HD, especially intra-abdominal infections leading to pancreas loss and vascular thrombosis [17], whereas a recent study found that pre-SPKT modality of dialysis did not influence the patient or graft survival nor did it increase the risk for surgical complications in SPKT patients [18]. In studies focusing solely on intra-abdominal infections after SPKT, no difference was detected between PD and HD patients [19,20] but the opposite results have been reported previously, with PD as a predisposing factor [21]. PD is still considered a contraindication for SPKT in some centers.

The primary aim of this study was to assess whether dialysis modality affects the risk for early postoperative complications in SPKT recipients.

Material and Methods

We conducted a retrospective longitudinal cohort study at our institution, in which pancreas transplantations were started in 2010. All consecutive recipients of pancreas transplantation between 2010 and 2017 were analyzed. Patient data were collected from the Finnish Transplant Registry, which is a national registry for the follow-up of kidney transplant patients, as required by law, and electronic patient records.

All transplantations were ABO-compatible and cytotoxic cross-match-negative. Immunosuppression comprised tacrolimus, mycophenolate, and steroids. All patients received induction with single-dose antithymocyte globulin before transplantation. The post-transplantation trough level target for tacrolimus was 12–15 ug/ml for the first 14 days and 10–12 ug/ml for days 15–90 after transplantation. All transplantations were performed using enteric proximal jejunal exocrine drainage. The peritoneal catheter was always removed during surgery. Thrombosis prophylaxis was performed with dalteparin 2500 IU twice daily for the first 14 postoperative days and 2500 IU once daily for the next 14 days. This study was approved by the Institutional Review Board of Helsinki University Hospital (HUS/269/2017).

Complications occurring during the first 3 months after transplantation were included. Post-transplantation pancreatitis and its severity was determined using the revised Atlanta classification [22]. Intra-abdominal infections were defined as the development of infected fluid collection that required an intervention. The administration of anti-bacterial drugs without intervention was not included in this category. Among patients on PD, data on history of preoperative peritonitis were gathered to analyze the possible association with post-transplant intra-abdominal infections. Gastrointestinal bleedings were defined as bleedings requiring relaparotomy or endoscopy, or patients suffering from sudden anemia combined with either melena or hematemesis. Other bleedings, consisting of intra-abdominal hemorrhages, were diagnosed by CT scan or relaparotomy performed due to acute anemia.

The statistical analyses were done comparing patients in the PD group and HD group. Survival probabilities were estimated using the Kaplan-Meier method, with death with functioning graft, pancreas graft failure, and kidney graft failure as the events. Non-parametric statistical analyses were performed, as all distributions were not normal. Categorical data were analyzed using Fisher's exact test, and continuous variables were analyzed using the Mann-Whitney U test. Two-sided P value <0.05 was considered as statistically significant. The calculations were performed using IBM SPSS Statistics (version 21, IBM Corporation, Somers, NY). Data are expressed as mean ±1 standard deviation.

Results

From March 2010 to December 2017, 101 pancreas transplantations were performed: 99 patients received SPKT and were
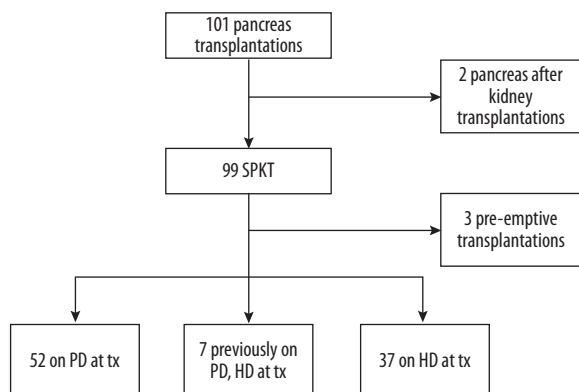
Figure 1. Flow-chart of the patients included.
SPKT – simultaneous pancreas and kidney transplantation; HD – hemodialysis; PD – peritoneal dialysis; Tx – transplantation.

all included, and 2 patients who received pancreas after kidney transplantation (PAK) were excluded. Before transplantation, 59 patients had a history of PD: 52 patients were on PD at the time of transplantation, 7 patients were previously on PD but were converted to HD, and 37 patients had been exclusively on HD. Pre-emptive transplantations (n=3) were not included in the comparative analysis (Figure 1).

There were no significant differences between the HD group and PD group regarding baseline characteristics such as recipient age, BMI, diabetes duration, dialysis duration, HLA-mismatch,

or cold ischemia time. Also, donor characteristics were similar between groups. The mean follow-up time was 29±20 months for the HD group and 32±22 months for the PD group (Table 1).

During the follow-up, 3 patients died, all in the PD group. The causes of death were myocardial infarction 45 months after transplantation, pulmonary embolism 8 months after transplantation, and complicated atypical mycobacterial infection combined with pancreatitis of the patient's native pancreas, which occurred 4 months after transplantation. All other kidney transplants were functioning at end of follow-up. Three pancreas grafts were removed due to infectious causes within 2 months after transplantation – 2 in the HD group and 1 in the PD group; these 3 patients were all alive with a functioning kidney graft at the end of follow-up. No significant differences were detected in kidney or pancreas graft or patient survival between the groups. Pancreas graft survival data are shown in Figure 2. Five patients developed insulin resistance during follow-up: 4 patients were managed by oral diabetes medication (metformin or sitagliptin) and 1 patient required exogenous insulin therapy.

All early postoperative complications are compared in Table 2. There were no significant differences in the frequency of complications between the HD and PD groups.

After transplantation, 9 patients had an intra-abdominal infection, with no significant difference between HD and PD groups (8% *vs.* 10%). Microbiological diagnosis was reached in all 9 cases; there were 4 bacterial infections, 1 fungal infection,

Table 1. Pretransplant recipient and donor characteristics.

|	HD (n=37)	PD (n=59)	P-value
Follow up time (months)	29±20	32±22	0.46
Recipient age (years)	42±9	43±8	0.39
Recipient BMI	25±3	24±2	0.16
Diabetes duration (years)	32±9	33±8	0.74
Dialysis duration (months)	13±9	13±8	0.74
Donor age (years)	40±13	38±13	0.35
Donor BMI	24±2	24±3	0.51
HLA AB mismacht	2.7±1.0	2.7±1.0	0.84
HLA DR mismatch	1.5±0.7	1.4±0.6	0.23
Kidney cold ischemia (hrs)	10.2±1.9	10.1±1.9	0.89
Pancreas cold ischemia (hrs)	8.1±1.8	8.2±1.9	0.76
Length of hospital stay (days)	21±9	22±15	0.72
1 Year creatinine (mg/dL)	1.2±0.3	1.3±0.4	0.46
End of follow up creatinine (mg/dL)	1.3±0.7	1.2±0.4	0.39
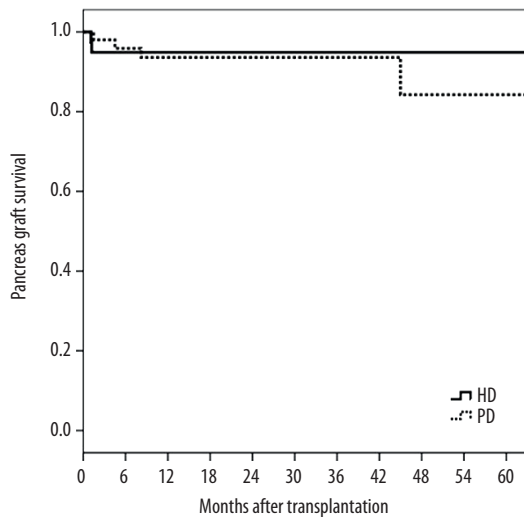
Figure 2. Pancreas graft survival (N=96, p=0.59). Kaplan-
Meier estimates for pancreas graft survival.
HD – hemodialysis; PD – peritoneal dialysis.

and 4 were cultured positive for both bacteria and fungi. Intra-abdominal infection was complicated with graft pancreatitis in 7 cases (HD group 8% *vs.* PD group 7%) and relaparotomy was required. Additionally, 2 patients, both in the PD group, had a wound infection that required vacuum-assisted closure and antibiotic therapy.

We analyzed also the impact of previous peritonitis among PD patients. Fifteen patients had a history of peritonitis during dialysis, with 7 patients experiencing 2 or more episodes. History of peritonitis was not associated with increased risk of complications, as after transplantation only 1 of these patients had an intra-abdominal infection and 1 patient had mild pancreatitis. Among patients converted from PD to HD (n=7), 3 were converted because of recurrent peritonitis, 3 had a pleuroperitoneal leak, and 1 had insufficient ultrafiltration. No differences were recorded in surgical conditions or time of surgery between patients with or without history of peritonitis (data not shown).

Relaparotomy rates were similar between groups (27% in the HD group and 24% in PD group). When the reasons for relaparotomy were analyzed, gastrointestinal bleedings (11% in HD group *vs.* 5% in PD group), other major bleedings (5% in HD group *vs.* 8% in PD group), and intra-abdominal infections (8% in HD group *vs.* 7% in PD group) were identified as the main causes. All indications for relaparotomy are summarized in Table 2.

The rate of bleeding complications was also similar between the groups. A nonsignificantly higher proportion of HD patients experiencing gastrointestinal bleeding compared to PD patients (22% *vs.* 10%, p=0.15) was identified. Other major bleedings (8% in HD group and 17% in PD group) consisted mostly of hematomas (in 8/13 patients) surrounding the renal transplant.

Table 2. Comparison of complications after pancreas-kidney transplantation between patients on hemodialysis (HD) or peritoneal dialysis (PD) before transplantation.

	HD (n=37)		PD (n=59)		P-value
Delayed graft function	5	(14%)	5	(9%)	0.5
Biopsy-proven acute rejection					
Kidney	4	(11%)	4	(7%)	0.7
Duodenum	6	(16%)	3	(5%)	0.08
Pancreas	2	(5%)	2	(3%)	0.64
Relaparotomy	10	(27%)	14	(24%)	0.81
Intra-abdominal infection	3	(8%)	4	(7%)	
Pancreatitis	0	(0%)	2	(3%)	
Gastrointestinal bleeding	4	(11%)	3	(5%)	
Other bleeding	2	(5%)	5	(8%)	
Ureteral stricture	1	(3%)	0	(0%)	
Gastrointestinal bleeding	8	(22%)	6	(10%)	0.15
Other major bleeding	3	(8%)	10	(17%)	0.36
Intra-abdominal infection	3	(8%)	6	(10%)	1.0
Pancreatitis	6	(16%)	10	(17%)	1.0
Mild	2	(5%)	2	(3%)	
Moderate	3	(8%)	5	(9%)	
Severe	1	(3%)	3	(5%)	

No differences were detected between groups when the rates of acute rejection or delayed graft function (DGF) were compared between the groups (Table 2). None of the patients had graft thrombosis.

Discussion

There are large worldwide differences in the usage of PD. In countries belonging to the ERA-EDTA (European Renal Association – European Dialysis and Transplant Association) registry, the prevalence of PD varies from 3.7% to 21.9% among patients on long-term dialysis [23]. In these countries, the prevalence of PD has been declining, although initiating PD was associated with improved patient survival compared to HD [24]. Also, in the United States, the use of PD has been declining, with 10% of patients on long-term dialysis currently being treated with PD [25]. In Finland, according to the latest report, the prevalence of PD is 19% of patients on long-term dialysis [26].

When evaluating patients undergoing SPKT, in our study, 62% (59/96) of patients had a history of PD before transplantation. This high incidence could be due to the fact that SPKT patients are younger and healthier compared to all ESRD patients, and they often choose a home dialysis modality as an autonomous method of renal replacement therapy. Center experience, geographical factors, and possible vascular problems also have an impact when choosing between HD and PD. In other studies, the percentage of patients on PD before SPKT is reported to be 25–41% [17,18,20].

Our study showed no significant differences in postoperative complications among patients undergoing SPKT when comparing HD or PD as pretransplant dialysis modalities. The rate of intra-abdominal infections, relaparotomies, pancreatitis, bleeding complications, and graft rejection were similar between groups. Graft survival was also similar between HD and PD groups, with 3 pancreas grafts removed due to infectious causes (2 in the HD group and 1 in the PD group). Although all 3 deaths occurred in the PD group, one was due to pulmonary embolism and another was due to myocardial infarction; these deaths occurred late after transplantation and were evaluated as unrelated to previous dialysis modality.

The effect of dialysis duration on mortality in ESRD patients is discussed with variable results. According to many studies, within the first year or two of dialysis, PD is associated with superior survival over HD, whereas in the longer term, PD is associated with comparable or increased mortality rates [27–29]. In our study, both groups had moderately short mean dialysis times before transplantation.

Controversy exists in previous studies about whether PD is a risk factor for intra-abdominal infections. Some studies report no difference between dialysis modalities [18–20], whereas other studies suggest that PD may be a risk factor for intra-abdominal infections in SPKT patients [17,21]. Our results showed no difference between groups with regard to intra-abdominal infections (8% for HD and 10% for PD). Furthermore, no increased risk for intra-abdominal infections was seen among patients with a previous history of peritonitis or in patients with several episodes of past peritonitis.

Another feared complication often leading to pancreas graft loss after transplantation is graft thrombosis. Some studies suggest PD as a risk factor for graft thrombosis among kidney transplant recipients [15,16]. In a recent study comparing SPKT patients, a higher relaparotomy rate due to graft thrombosis was detected in the PD group [17]. In our study, none of the patients experienced graft thrombosis. Our strategy of using an aggressive approach with postoperative anticoagulation could be the reason for the lack of thrombosis, but increasing the risk for bleeding complications, which were relatively frequent in our cohort.

Our study has some limitations that should be considered. As our center is the only transplant center in Finland, this a single-center study, although it represents a whole nation-wide cohort. In addition, no specific rating system was used to rate our donors, which makes comparison to other centers somewhat difficult. Therefore, these results may not be applicable to other transplant populations. On the other hand, our findings support the findings of recent studies suggesting that PD is a safe dialysis modality, even among patients waiting for SPK transplantation. In addition, our study is limited by the small number of patients. The strengths of our study include the high frequency of PD treatment in our country, and the fact that both PD and HD groups were very similar with regard to baseline characteristics. In addition, all patients received a transplant within a short time period, during which no other changes occurred in treatment policies.

Conclusions

We found that peritoneal dialysis was not a risk factor for postoperative complications after simultaneous pancreas-kidney transplantation, even among patients with a history of peritonitis, and the pretransplant dialysis modality was not associated with patient or graft survival. Our findings, together with the previous literature, suggest that peritoneal dialysis is a safe dialysis modality for patients waiting for pancreas transplantation.

Conflicts of interest

None.

ORIGINAL PAPER

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