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Simultaneous pancreas-kidney transplantation: Initial experience of a center in Japan

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ABSTRACT

Background: Simultaneous pancreas-kidney transplantation (SPK) is an established therapy for diabetes mellitus (DM) patients with associated end stage renal disease. We report the initial results of SPK in our institution after qualification as transplantation program.

Patients and methods: Between September 2017 and July 2018, we performed 3 SPK in type 1 diabetic patients with end-stage renal disease. All grafts were procured from brain-dead marginal donors according Pittsburg criteria.

Results: The recipients were 2 men and 1 woman with a mean age of 43 ± 5.4 years. Mean time from DM diagnosis and time on dialysis were 25.7 ± 3.9 years and 19.7 ± 9.1 months. The mean age and HbA1C value of donor were 56.7 ± 0.5 years and 5.67 ± 0.05%. The pancreatic grafts were transplanted intraperitoneally in the right iliac fossa. Two patients required a relaparotomy due to arterial anastomotic hemorrhage and two patients developed acute cellular rejection. With a median follow-up of 13 (6–15) months, patient's and graft's survival rate were 100%. All patients showed HbA1C within normal range, but oral glucose tolerance test showed DM pattern in two patients at 3 months after transplantation.

Conclusions: In our initial experience with SPK, mid-term grafts and patient survival appear comparable to the results reported in literature. Despite the limited availability of donors and the use of grafts from marginal donors, a quality pancreas transplantation program can be established even in a small-volume centers. Nonetheless further improvement in surgical techniques and meticulous management appear mandatory.

1. Introduction

Simultaneous pancreas-kidney transplantation (SPK) is an established treatment for type 1 diabetic patients with end-stage renal disease [1]. The outcome of SPK has improved thanks to significant advances in surgical technique [2], preservation methods [3,4] and immunosuppression regimens [4]. Nonetheless pancreas graft is still associated with a significant burden of early severe complications, including thrombosis (prevalence 10–20%), graft duodenal perforation (%) and acute cellular rejection (20% within the first year) which are associated with high risk of graft loss (REF).

In Japan, the annual number of brain death donors has dramatically increased thanks to the revision of the law on organ Transplantation in 2010. However, the rate of organ donation is currently about 70–80 cases per year, which is far less than in other countries. Due to such severe shortage of donations, the annual number of pancreas transplantation in Japan is around 35 cases compared to over 200 candidates on transplant waiting list. In the United States, more than 65% of

Abbreviations: SPK, Simultaneous pancreas-kidney transplantation; DM, Diabetes mellitus; r-ATG, anti-thymocyte globulin (rabbit); ACR, Acute cellular rejection; AMR, Antibody mediated rejection; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; APTT, activated partial thromboplastin time; OGTT, oral glucose tolerance test

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waiting patients is transplanted within 1 year [5], while in Japan, the median waiting time for pancreas transplantation is around three and half year and a nearly 25% of patients have been waiting more than 5 years [6].

Under such circumstances, it is expected that the development of a new pancreas transplantation program in a small volume center may face several difficulties.

Our Institution has performed 285 cases of liver transplantation and 258 case of kidney transplantation, since the brief case respectively in 1997 and 1965 until now. Between September 2017 and July 2018, we performed 3 cases of SPK in type 1 diabetic patients with end-stage renal disease.

On October 2016 Our Institution received the certification as 18th facility for pancreas transplantation in Japan and between September 2017 and July 2018, we performed 3 cases of SPK. The aim of the present study was to report the result of our initial experience

2. Patients and methods

Clinical and demographic characteristics of recipients and donors as well as data about transplant surgical procedure and postoperative course were retrospectively reviewed after approval by the ethical committee of Nagasaki university hospital (#15052506).

Selection criteria for SPK indication were DM type 1 associated with end-stage renal disease in dialysis therapy.

All grafts were procured from brain-dead donors and were preserved with University of Wisconsin solution.

Pancreas was implanted intraperitoneally in the right iliac fossa trough a modified hockeystick incision. Graft artery and portal vein were respectively anastomosed to the recipient's external iliac artery and vein. A Carrel patch and a Y-graft were employed in 2 and 1 case respectively. After bringing a jejunal limb, graft exocrine drainage was provided by anastomosis of the duodenum graft to a Roux-en-Y jejunal limb in a side-to-side fashion by two-layer continuous running suture.

Kidney was implanted retroperitoneally in the left iliac fossa, with anastomosis of graft renal artery and vein to recipient's external iliac artery and vein respectively. Ureter was anastomosed to the urinary bladder using Lich-Gregoir standard technique.

Immunosuppression protocol was based on induction with basiliximab and maintenance with calcineurin inhibitor (CNI), mycophenolate mofetil (MMF) and steroid.

Thromboprofilax protocol was based on intravenous heparin infusion. It was started during transplantation at kidney graft reperfusion and was maintained until POD 10. Thereafter it was switched to low dose aspirin. Target range of activated partial thromboplastin time (APTT) during heparin infusion was between 45 and 60 s. For antimicrobial perioperative prophylaxis, third generation cephalosporin and micafungin sodium 100 mg were given for 3 and 7 days respectively. CMV prophylaxis was not routinely used.

After hospital discharge all the patients were followed up clinically and monitored for grafts function by physical examination and laboratory test for fasting glucose, HbA1C, C-peptide, amylase, lipase, creatinine and anti-CMV pp65 antibody. In additionally oral glucose tolerance test (OGTT) was performed periodically.

3. Results

The recipients were 2 men and 1 woman, with a mean age of 43 ± 5.4 years, HbA1C value of 8.1 ± 1.1%, the duration of DM of 25.7 ± 3.9 years and time on dialysis of 19.7 ± 9.1 months. According to the Minnesota criteria [7] and Pittsburg criteria [8], all donors were classified as marginal donors. The mean donor age was 56.7 ± 0.5 years, body mass index 22.9 ± 1.3 kg/m^2. In two donors, the cause of death was cerebrovascular disease while for all of the donors a cardio-pulmonary arrest was reported. All of donors used at least two types of vasopressors. The mean HbA1C and serum creatinine value were 5.67 ± 0.05% and 0.62 ± 0.11 mg/dl respectively. The mean number of HLA mismatch was 3.7 ± 1.2. The characteristics of donors and recipients were summarized in Table 1.

Table 1
Characteristics of donor and recipient (n = 3).

Characteristics	value
Recipient	
Age (yr)	43 ± 5.4
Gender (male, female)	2:1
HbA1C	8.1 ± 1.1
Duration of diabetes (yr)	25.7 ± 3.9
Duration of dialysis (mo)	19.7 ± 9.1
Donor	
Age (yr)	56.7 ± 0.5
Gender (male, female)	1:2
Body mass index (kg/m^2)	22.9 ± 1.3
Cause of death	
Cerebrovascular disease	2 (66.6%)
Hypoxic brain damage	1 (33.3%)
Pre-procurement HbA1C (%)	5.67 ± 0.05
Pre-procurement creatinine (mg/dl)	0.62 ± 0.11
Marginal donor	
Minnesota criteria	3 (100%)
Pittsburg criteria	3 (100%)
HLA mismatch	3.7 ± 1.2

The mean total ischemia times was 597 ± 110 min for the renal grafts and 841 ± 95 min for the pancreatic grafts. The implantation time for pancreas and kidney were 316 ± 13 and 258 ± 27 min respectively. Mean blood loss was 1032 ± 246 gr.

The postoperative course of each patient was summarized in Table 2. Three episodes of acute bleeding requiring relaparotomy occurred in 2 patients within POD 1. No hemodynamic instability was associated. At surgical exploration the source of bleeding was the pancreas arterial anastomosis in 2 cases and kidney arterial anastomosis in 1 case. Thereafter, one patient developed a peripancreatic abscess without any signs of pancreatic leak or duodenal perforation, which was treated with surgical toilette.

No cases of pancreas graft trombosis, ileus, delayed graft function of the kidney, or urologic complications were recorded.

Two patients developed an episode of acute cellular rejection (ACR) at POD 30 and 49 respectively. In one patient, rejection affected only the kidney while in the other it was combined pancreas-kidney. Both patients were treated with steroid pulse and r-ATG with normalization of laboratory tests. However, in the recipient who developed a combined kidney-pancreas ACR, a CMV infection occurred during r-ATG therapy. Therefore, intravenous ganciclovir and intravenous gammaglobulin were administered and the immunosuppression was tapered. No cases of antibody-mediated rejection were recorded.

The mean HbA1C and serum creatinine level at 1, 3, 6, 12 months after transplantation were 5.1 ± 0.2%, 5.2 ± 0.2%, 5.5 ± 0.1% and 5.5 ± 0.1% and 1.3 ± 0.2 mg/dl, 1.4 ± 0.2 mg/dl, 1.4 ± 0.2 mg/dl and 1.6 ± 0 mg/dl.

Despite of a normal HbA1c, two patients showed DM pattern at OGTT at 3 months after transplantation. The mean HOMA-IR at 3 and 12 months after transplantation were 0.98 ± 0.35 and 0.87 ± 0.27. The mean HOMA-β at 3 and 12 months after transplantation were 36.1 ± 10.9 and 48.3 ± 20. Trends of HOMA-IR and HOMA-β were summarized in Fig. 1A and B. In the glucagon stimulation test, all patients showed ΔCPR ≥ 2 at any time. With a median follow-up of 13 [6–15] months, patient's and all graft's survival rate were 100%.

4. Discussion

Due to the significant shortage of deceased donor in Japan, up to 63% of pancreas grafts are currently obtained from marginal donors according Pittsburg criteria [8,9]. Indeed, all the donors in the present

Table 2
Postoperative course of the recipients.

	Total	Patient 1	Patient 2	Patient 3
Surgical complications				
Bleeding	2 (66.7%)	Pancreas arterial anastomosis POD 1	None	Pancreas arterial anastomosis POD 0 Kidney arterial anastomosis POD 1
Surgical site infection	2 (66.7%)	Subcutanous abscess POD 8	None	Peripancreatic abscess POD 11
Pancreas graft thrombosis	0	None	None	None
Duodenal perforation	0	None	None	None
Graft rejection				
Pancreas ACR	1 (33.3%)	None	POD 49 Treated with steroid pulse + *r*-ATG therapy	None
Kidney ACR	2 (66.7%)	POD 30 Treated with steroid pulse and r-ATG therapy	POD 49 Treated with steroid pulse + *r*-ATG therapy	None
AMR	0	1 (33.3%)	None	None

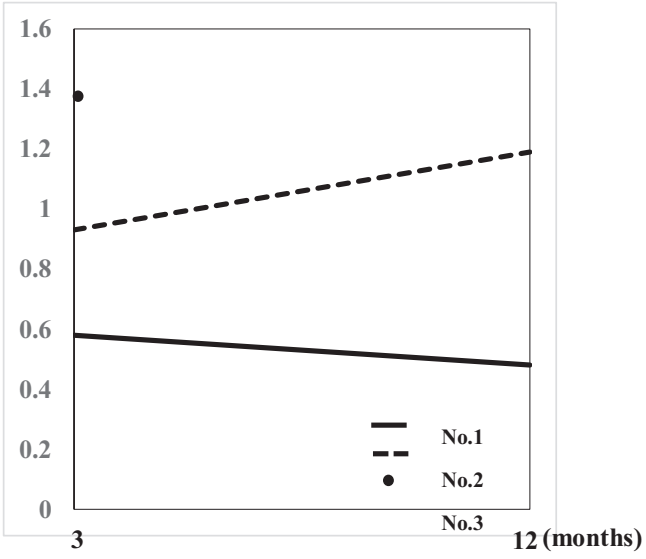

Fig. 1. A: All patients showed normal value of HOMA-IR at 3 and 12 months after transplantation. **B:** Two patients showed low value of HOMA-β at 3 months after transplantation and did no improved thereafter.

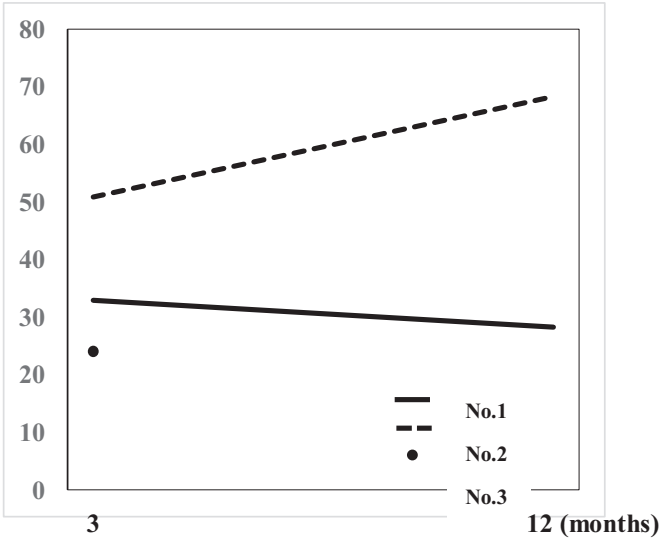

Fig. 1. (*continued*)

clinical series were classified as marginal. Such characteristics may potentially compromise the outcome of SPK [6,8]. In our series, two patients showed a negative trend of HOMA-β during the follow-up which may be due to a low graft quality from marginal donors. These patients may require dipeptidyl peptidase-4 inhibitors in the future for beta cell protection and insulin secretion promotion. Furthermore, it has been reported that grafts from marginal donors are associated with an increased risk of pancreas graft thrombosis and graft loss [10,11]. Other identified risk factors for graft thrombosis comprise vascular injury during organ procurement, quality of preservation and reperfusion, surgical technique [12], decrease in flow rate of drainage vein [13] and hyper coagulated state after surgery [14]. With the aim to minimize the risk of graft thrombosis, the selected thromboprofilax protocol at our Institution was based on intraoperative start of intravenous heparin infusion for the first 10 postoperative days, as modified protocol of previous report [15]. However, this management was surely associated with a higher hemorrhagic risk which was the probable cause of the 3 cases of early postoperative hemorrhage requiring relaparotomy in the present series. Nonetheless, no hemodynamic instability was associated, the prompt surgical bleeding control resulted effective and at a mean follow up time of 13 months all the grafts are well functioning.

The other main concern of the present clinical series was ACR. The overall prevalence of kidney ACR in our institution was 8.9% which appears to be in line with the data as reported [16]. In our series, all patients were inducted by basiliximab and in two of three patients developed ACR, such results may be clinically significant and require any immunosuppresive protocol change for the moment. Compared basiliximab and r-ATG, r-ATG had an effect to decrease the acute cellular rejection in the first year after SPK with similar side effects as an induction therapy [17]. Besides r-ATG is not covered by health insurance in Japan at the moment. Anyway, new cases of SPK will surely provide additional data. Nonetheless ACR of pancreas graft is associated with increased risk for not only acute but also chronic graft loss. In the single case of ACR of the present series, the graft recovered completely after administration steroid pulse and r-ATG, but longer follow-up will be needed for evaluation of long-term outcome.

In our initial experience with SPK, mid-term grafts and patient survival appear comparable to the results reported in literature. Despite the limited availability of donors and the use of grafts from marginal donors, a quality pancreas transplantation program can be established even in a small-volume centers. Nonetheless further improvement in surgical techniques and meticulous management appear mandatory.

Disclosure

The authors declare no conflicts of interest in association with the present study. Ono S contributed to this paper.

- S.O. participated in making the study concept and design, collecting data, performing the literature review and drafting the manuscript.
- T.A., M.H., M.T. and S.E. participated in making the study concept and design, collecting data and reviewing the manuscript.
- K.A., Y.M., R.P., M.S. and K.K. participated in reviewing the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tpr.2019.100029.

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