Outcome of surgical complications following simultaneous pancreas–kidney transplantation

Neal Banga, Vassilis G. Hadjianastassiou, Nizam Mamode, Francis Calder, Jonathon Olsburgh, Martin Drage, Cinzia Sammartino, Geoff Koffman and John Taylor

Department of Transplantation, Guys and St Thomas’ NHS Foundation Trust, London, UK

Correspondence and offprint requests to: Vassilis G. Hadjianastassiou; E-mail: vassilis@doctors.org.uk

Abstract

Background. Simultaneous pancreas–kidney (SPK) transplantation carries a higher risk of surgical complications than kidney transplantation alone. We aimed to establish the incidence of surgical complications after SPK transplantation and determine the effect on graft and patient survival.

Methods. Outcomes of all SPK transplants performed at our centre were compared between patients who experienced a surgical complication (SC group) and those who did not (NSC group).

Results. Our centre performed 193 SPK transplants in a 15-year period; 44 patients (23%) experienced a surgical complication. One-year and 5-year pancreatic graft survival was 89 and 80%, respectively; this was lower in the SC group. There was no significant difference in patient or kidney graft survival between the SC and NSC groups at 5 years (92 and 83%, respectively.)

Conclusion. Surgical complications following SPK transplantation can cause significant morbidity and adversely affect pancreas graft survival, but do not affect long-term kidney or patient survival.

Keywords: pancreas transplantation; surgical complications

Introduction

Simultaneous pancreas–kidney (SPK) transplantation is the gold standard treatment for patients with end-stage renal failure secondary to insulin-dependent diabetes mellitus (DM) who are fit enough to undergo major surgery [1]. The operation can improve their quality of life [2] and life-expectancy compared with kidney transplantation alone (KTA) [3]. However, SPK transplantation is a more complex operation than KTA, with longer hospital stay and higher morbidity [4].

SPK transplantation is usually performed via a midline laparotomy, providing access to the iliac vessels bilaterally; a schematic diagram is shown in Figure 1. The pancreas graft’s superior mesenteric artery and splenic artery (using an interposition ‘Y’ graft of donor iliac vessels) are anastomosed to the recipient right common iliac artery and the graft portal vein is anastomosed to the right common iliac vein or inferior vena cava [1]. An alternative technique is portal venous drainage (to achieve ‘physiological’ insulin delivery) by anastomosis of the graft portal vein to the recipient superior mesenteric vein [5]. Management of the pancreatic exocrine drainage is achieved by pancreaticoduodenal transplantation with either bladder [6] or more commonly enteric drainage [7], with a side-to-side anastomosis of the donor duodenum onto the dome of the recipient bladder or distal small bowel, respectively. The renal allograft is then anastomosed to the left external iliac vessels and bladder in the usual fashion [8].

Pancreas transplantation in the UK is commissioned at a national level to guarantee adequate funding and quality control. Our centre is one of eight in the UK performing SPK transplantation. We report the incidence of surgical complications following SPK transplantation in our centre since the inception of the programme and their effect on graft and patient survival.

Materials and methods

Potential recipients for an SPK transplant were assessed for their suitability by a consultant transplant surgeon and nephrologist, according to published national UK guidelines [9]. Patients considered for SPK transplantation were those below the age of 60 years with insulin-dependent DM either with or approaching end-stage renal failure (estimated glomerular filtration rate ≤20 mL/min/1.73m²). The symptom of hypoglycaemic unawareness was an urgent indication for prompt referral by their physician. All patients underwent cardiovascular assessment in the form of exercise electrocardiogram, stress echocardiogram or myocardial perfusion scan proceeding to coronary angiography if appropriate.

All SPK transplants were performed from cadaveric donors, and donor selection criteria included age ≤60 years, body mass index <30 kg/m² and estimated cold ischaemic time (CIT, the time from cold perfusion of organs in the donor to the organs being removed from cold storage in the recipient operation) <18 h. Until 2007, only organs from DBD (donation after brainstem death or ‘heart-beating’) donors were accepted. In line with national trends, organs from DCD (donation after cardiac death or ‘non-heart beating’) donors have been accepted since 2007.

In our centre, vascular reconstruction was performed as shown in Figure 1. Arterial reconstruction was performed using the donor iliac artery ‘Y’ graft; no interposition graft was used for the venous anastomosis. From 1996 until 2005, the recipient bladder was used for pancreatic exocrine
Surgical complications after SPK transplantation

Drainage; enteric drainage was used from 2006 onwards. In both cases, a two-layer side-to-side anastomosis with a continuous absorbable suture was used, and the ends of the donor duodenum were closed with a linear stapler, over-sewn with a continuous absorbable suture. Closed non-vacuum abdominal drains were routinely placed.

Immunosuppression since 1999 has consisted of basiliximab induction with a triple-agent maintenance regime (tacrolimus, mycophenolate mofetil and prednisolone). Prior to 1999, anti-thymocyte globulin was used as an induction agent, with a maintenance regime of tacrolimus or cyclosporine with azathioprine and prednisolone. Subcutaneous heparin thromboprophylaxis (5000 U twice daily) was prescribed for all patients post-operatively until discharge.

This is a retrospective study of all SPK transplants performed at our centre; all data were recorded on to a computerized database. All patients were reviewed in our centre for a minimum of 3 months post-transplantation. Outcomes (immediate post-operative, 1-year and 5-year) were compared between patients who experienced a surgical complication (SC group) and those who did not experience a surgical complication (NSC group). A surgical complication was defined as the need for re-laparotomy within 3 months of the transplantation. Pancreas graft failure was defined as the permanent requirement for exogenous insulin after transplantation. 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 pre-transplant renal function. 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. Patient survival was determined as time from first transplant to time of patient death, censoring at last follow-up where no death was reported.

Statistical analysis was performed using ‘Statistical Package for the Social Sciences’ version 12 for Windows® (SPSS, Chicago, IL). Categorical data were analysed using the chi-squared or Fisher’s exact test. Continuous data were analysed using the Mann–Whitney U-test. Survival after transplantation was examined using Kaplan–Meier survival curves with the log-rank test for survival difference between groups. Statistical significance was set at a P-value of <0.050.

Results

Between August 1996 and February 2010, 193 patients underwent SPK transplantation in our centre. Median (range) recipient age was 39 (15–58) years, and 25% of patients were pre-dialysis, with no significant difference in the number of pre-emptive transplants between the NSC and SC groups (Table 1). Median daily insulin requirement was similar between the NSC and SC groups (42 versus 40 U, P = 0.094). Median (range) donor age was 32 (10–56) years, which was significantly higher in the SC group (37 versus 31 years, P = 0.014). Of the 193 donors, 185 (96%) were DBD donors. Median (range) CIT was 12 (8–22) h (pancreas) and 14 (10–24) h (kidney), with no significant difference between the NSC and SC groups (Table 1). There was no significant difference in the immunosuppressive regimen used between the two groups. Ninety-seven (50%) patients had bladder and 96 (50%) patients had enteric exocrine drainage (no significant difference between the NSC and SC groups, P = 1.000). Of the 97 bladder-drained patients, 12 (12%) subsequently underwent bladder to enteric conversion of exocrine drainage, to manage intractable urological or metabolic complications.

Of the 193 SPK recipients, 44 (23%) experienced one or more surgical complications, undergoing a median (range) of 2 (1–36) post-transplant laparotomies. The principal indication for re-laparotomy in these patients is shown in Table 2. At laparotomy, 26 patients were found to have intra-abdominal collections, with an obvious donor duodenal segment (DS) leak identified in 7 of these. Five patients with DS leak were managed by laparotomy and washout with suture repair (with or without omental patch) of the leak, although this was unsuccessful in 1 patient, who subsequently required a defunctioning proximal jejunostomy. The other two patients with DS leak had necrosis of the DS and underwent graft pancreatectomy. Three patients underwent graft pancreatectomy for graft portal venous thrombosis. Six patients required a repeat laparotomy for haemorrhage, one of whom underwent graft pancreatectomy. Therefore, a total of 6/193 patients (3%) underwent graft pancreatectomy, and in addition, 4/193 patients (2%) underwent transplant nephrectomy in the first 3 months post-transplantation. Overall, median (range) hospital stay was 18 (7–340) days, and this was significantly higher in the SC group (46 versus 16 days, P < 0.001).

<table>
<thead>
<tr>
<th>Table 1. Donor, recipient and operative data</th>
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<tbody>
<tr>
<td>SC group</td>
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<td>--------</td>
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<tr>
<td>n</td>
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<tr>
<td>Recipient age (years)</td>
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<tr>
<td>Recipient on dialysis</td>
</tr>
<tr>
<td>Donor age (years)</td>
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<tr>
<td>DBD donor</td>
</tr>
<tr>
<td>Pancreas CIT (hours)</td>
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<tr>
<td>Kidney CIT (hours)</td>
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<tr>
<td>Enteric exocrine drainage</td>
</tr>
</tbody>
</table>

*Continuous data are shown as median (range). SC = surgical complication group, NSC = no surgical complication group, DBD = donation after brainstem death. The bold type indicates statistical significance.*
Of 44 patients who underwent re-laparotomy, 12 required a laparostomy for management of infective complications and/or prevention of abdominal compartment syndrome. Our current practice is to manage the laparostomy using negative pressure dressings. In 10/12 of these patients, the laparostomy was allowed to heal by secondary intention, with subsequent skin grafting in appropriate cases. Five patients developed a pancreatic or enterocutaneous fistula; in three patients, these were managed non-operatively.

Only 4/193 patients had primary non-function of the pancreas graft (in three cases due to graft portal venous thrombosis). Pancreatic delayed graft function (requirement for exogenous insulin in the immediate post-transplant period) was rare, occurring in only one patient. Primary non-function of the kidney occurred in only two patients. The overall rate of kidney delayed graft function (requirement for dialysis in the first week post-transplantation or in predialysis patients, failure of the serum creatinine to fall by 10% in the first 24 h) was 17%, and this was higher in the SC group (23 versus 16%, \( P = 0.017 \)).

Overall, 1-year pancreatic graft survival was 89%, and this was significantly lower in the SC group compared to the NSC group (77 versus 93%, \( P = 0.001 \)). Overall 1-year kidney survival was 93%, and this was also significantly lower in the SC group (86 versus 96%, \( P = 0.027 \)). Overall 1-year patient survival was 97%, with no difference between the SC and NSC groups. Overall 5-year pancreas survival was 80%, and this was lower in the SC group (74 versus 82%, \( P = 0.027 \)), as shown in Figure 2. Overall 5-year kidney survival was 83% and 5-year patient survival was 92%, without significant differences between the SC and NSC groups, as shown in Figures 3 and 4. Complete 1-year and 5-year survival data are summarized in Table 3.

### Discussion

The first ever pancreas transplant was performed in 1966 at the University of Minnesota Hospital [10] and that institution has subsequently performed >2000 pancreas transplants, not only in the form of SPK transplantation but also pancreas transplantation alone (PTA) and pancreas after living-donor kidney (PALK) transplants. Approximately 200 pancreas transplantsations are performed each year in the UK, the majority of which are SPK transplantation (77% in 2008–09) [11].

There is ample evidence in the literature to suggest that SPK transplantation, by re-establishing glucose and insulin homeostasis, can prevent the recurrence of diabetic nephropathy in the kidney transplant [12], reduce the progression of retinopathy [13] and halt or reverse neuropathy [14].

### Table 2. Principal indication for re-laparotomy in the first 3 months post-transplant for 44 patients who experienced a surgical complication

<table>
<thead>
<tr>
<th>Principal indication for laparotomy</th>
<th>No. of patients</th>
<th>Graft loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal collection</td>
<td>26</td>
<td>Pancreatectomy—2</td>
</tr>
<tr>
<td>Pancreatic venous thrombosis</td>
<td>3</td>
<td>Pancreatectomy—3</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>6</td>
<td>Pancreatectomy—1</td>
</tr>
<tr>
<td>Ureteric complications</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Primary non-function of kidney</td>
<td>2</td>
<td>Transplant nephrectomy—2</td>
</tr>
<tr>
<td>Abdominal compartment syndrome</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Colonic perforation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>Graft pancreatectomy—6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transplant nephrectomy—4</td>
</tr>
</tbody>
</table>
Surgical complications after SPK transplantation

| Table 3. Cumulative 1-year and 5-year survival (number at risk in brackets)† |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
|                             | All patients    | SC group        | NSC group        | P-value         |
| Pancreas survival           |                 |                 |                 |                 |
| 1-year                      | 89% (160)       | 77% (38)        | 93% (122)       | **0.001**       |
| 5-year                      | 80% (72)        | 74% (18)        | 82% (54)        | **0.027**       |
| Kidney survival             |                 |                 |                 |                 |
| 1-year                      | 93% (162)       | 86% (38)        | 96% (119)       | **0.023**       |
| 5-year                      | 83% (70)        | 82% (16)        | 83% (54)        | 0.412           |
| Patient survival            |                 |                 |                 |                 |
| 1-year                      | 97% (163)       | 95% (39)        | 97% (124)       | 0.550           |
| 5-year                      | 92% (73)        | 93% (18)        | 92% (55)        | 0.928           |

†The bold type indicates statistical significance.

importantly, it can attenuate long-term cardiovascular disease [15, 16] and improve the quality of life of the recipients who no longer need to inject themselves with regular insulin, perform spot-checks of their blood glucose or sustain strict dietary habits [17].

An alternative to deceased donor SPK transplantation is a PALK transplant (transplantation of a deceased donor pancreas after a live donor kidney transplant) which has improved renal allograft survival compared to a cadaveric SPK transplant [18], although it has been claimed that this is at the expense of decreased survival for the pancreas graft [19]. For patients with Type I DM and end-stage nephropathy awaiting for or following a renal transplant, a promising alternative may be islet cell transplantation [20]. However, present, SPK transplantation is still widely accepted as the gold standard treatment, as outcomes after islet transplantation may be unreliable and sub-optimal [21].

Pancreas transplantation is reputed to carry the highest risk of surgical complications of all routinely transplanted solid organs [22], up to 43% [23]. Technical failures such as vessel thrombosis or DS complications are the most common cause of early graft loss [24]. The most common late causes of graft loss are immunological (i.e. rejection) and death with a functioning graft [25, 26].

The overall incidence of pancreas graft venous thrombosis in our centre was 3/193 (2%); the reported incidence of venous thrombosis is 2–14% [23, 27, 28, 29] and is thought to be due to a combination of factors including a hypercoagulable state [29], the low-flow circulation of the organ and anastomotic technical error [30]. Thromboelastograms are now used in some centres to guide peri-operative anticoagulation [31], although our current series suggests that routine subcutaneous heparin thromboprophylaxis appears to be a satisfactory protocol.

One of the main challenges in SPK transplantation is the successful management of pancreatic exocrine drainage, the techniques of which have evolved over the last 40 years [25]. The reported incidence of DS complications is 4–19% [27, 28, 32]. DS leakage of pancreatic secretions, urine or enteric contents (depending on the method of exocrine drainage) usually presents with fever, abdominal pain and hyperamylasaemia [32]. DS leakage most commonly occurs in the early post-operative period from the stapled ends of the donor duodenal stump [32], where the blood supply may be sub-optimal. From our 193 SPK transplant recipients 7 (4%) were found to have DS leak at laparotomy. However, a further 19/193 patients (10%) underwent laparotomy for post-transplant collections, and some of these may have been due to an occult DS leak. The reported incidence of re-operation for infected collections after SPK transplantation is 10% [23, 27, 28]. A leak from an enteric-drained pancreas graft usually necessitates laparotomy [28, 32] and can frequently result in graft pancreatectomy [22]. In our centre, 5/7 patients with DS leak were managed without graft pancreatectomy. Some surgeons advocate isolating the donor duodenum—recipient small bowel anastomosis by use of a roux-en-y loop [33] in an attempt to reduce the impact of a leak from an enteric-drained pancreas graft.

One advantage of bladder drainage is that a leak at the bladder–duodenal anastomosis may be managed conservatively with a urinary catheter [32, 34]. Another advantage is the ability to measure urinary amylase, a decline in which may indicate early graft rejection [1], although this is more important in PTA and PALK than SPK transplants, where the two organs are immunologically distinct [25]. However, there is a high incidence of recurrent urological complications in bladder-drained patients, such as urinary tract infection, haematuria and reflux pancreatitis, and chronic metabolic acidosis due to bicarbonate loss [35, 36]. In 2006, our centre followed the worldwide trend in a move from bladder drainage to enteric drainage, due to these complications. We have also performed 12 bladder-to-enteric conversions of exocrine drainage in patients that were originally bladder-drained, which is a safe and effective treatment for patients that experience these complications [37]. In our cohort of patients, an identical proportion of patients in the SC and NSC groups were bladder-drained and enteric-drained. There is no evidence in the literature to suggest that either technique reduces surgical complications, but some studies have shown improved graft survival for bladder-drained grafts [25, 35], others for enteric-drained grafts [38] and some have shown no difference in graft survival between the two methods [26, 36].

Aside from operative technique, donor and recipient factors may affect outcome after SPK transplantation. When comparing the SC and NSC groups, the only significantly different donor or recipient factor was a higher median donor age in the SC group (37 versus 31 years, P = 0.014). This correlates with other studies that show worse outcomes with increasing donor age [22, 25, 27]. We feel that the overall low rates of pancreas graft primary non-function and delayed graft function in our centre reflect our strict donor criteria.

In our centre, overall 1-year pancreas, kidney and patient survival were 89, 93 and 97%, respectively. Sutherland et al. [25] (University of Minnesota) reported 1-year pancreas, kidney and patient survival rates of 92, 88 and 92%, respectively; Sollinger et al. [26] (University of Wisconsin) reported survival rates of 88, 91 and 97%, respectively, at 1 year. Both of these American series included one thousand patients. With regard to long-term outcome, actual 5-year pancreas, kidney and patient survival in our centre were 80, 83 and 92%, respectively. Sutherland reported 4-year pancreas, kidney and patient survival of 82 (74% if enterically drained), 81 and 88%, respectively [25]; Sollinger reported 10-year survival as 63, 63 and 80%, respectively [26].
summary, the short- and long-term results of our centre are comparable to reports from high-volume American centres.

As expected, a surgical complication following SPK transplantation adversely affected 1-year pancreas (SC 77% versus NSC 93%, \( P = 0.001 \)) and kidney (SC 86% versus NSC 96%, \( P = 0.023 \)) survival, with the loss of six pancreas and four kidney grafts in the early post-operative period. This decrease in survival is attributable to early complications such as venous thrombosis, haemorrhage and primary non-function necessitating graft pancreatectomy/nephrectomy. Five-year pancreas survival was also lower in the group with surgical complications (SC 74% versus NSC 82%, \( P = 0.027 \)). However, as shown in Table 3 and Figure 4, patients who experienced a surgical complication had comparable 1-year and 5-year patient survival to those that did not. Contrary to reports in the literature that loss of the pancreas graft within the first year can adversely affect survival of the renal graft (60 versus 82% at 3 years, \( P < 0.001 \)) [39], patients in our centre who experienced a surgical complication had comparable 5-year kidney survival with patients who did not (82 versus 83%, \( P = 0.412 \)), as shown in Table 3 and Figure 3. Although technical failure of the pancreas transplant has serious ramifications for the patient, our results reveal that long-term kidney and patient survival remain unaffected. Pancreatic re-transplantation after SPK has similar results to PAK transplants and is a potential option for these patients [40].

This study provides what we believe to be the first account of the morbidity and mortality experienced in SPK transplantation in a UK centre. Surgical complications after SPK transplantation are common and may result in significant morbidity, adversely affecting pancreas graft survival, but encouragingly not affecting long-term kidney or patient survival.

Conflict of interest statement. None declared.

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Surgical complications after SPK transplantation


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