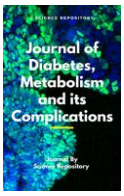

Available online at www.sciencerepository.org

Science Repository

Research Article

Enteric Leaks from Simultaneous Pancreas Kidney Transplantation at a Single Centre: Risk Factors and Management Over a 20-Year Period

Amy Hort[1], Sara Shahrestani[1], Kerry Hitos[1,2], Taina Lee[1], Richard Allen[1], Lawrence Yuen[1], Jerome Laurence[1,2,5], Brendan Ryan[1], Paul Robertson[1], Kathy Kable[1], Angela Webster, Germaine Wong[4], Natasha Rogers[4], Richard Allen[1], Phillip O'Connell[4], Brian Nankivell[4], Jeremy Chapman[4], Wayne J. Hawthorne[1,2,3] and Henry C. Pleass[1,2*]

[1]*The Department of Surgery, Westmead Hospital, Westmead, Australia*
[2]*Westmead Clinical School, The University of Sydney, Sydney, Australia*
[3]*The Centre for Transplant and Renal Research, Westmead Institute for Medical Research, Westmead, Australia*
[4]*The Department of Renal Medicine, Westmead Hospital, Westmead, Australia*
[5]*The Department of Surgery, Royal Prince Alfred Hospital, Sydney, Australia*

ARTICLE INFO

Article history:
Received: 15 August, 2020
Accepted: 27 August, 2020
Published: 5 September, 2020

Keywords:
Simultaneous pancreas kidney transplantation
enteric leaks
risk factors

ABSTRACT

Background: Simultaneous pancreas-kidney transplantation (SPK) remains the gold standard treatment for patients with type I diabetes mellitus and end-stage renal failure. Enteric drainage is utilised to handle exocrine secretions from the graft, with enteric leaks being the most challenging of complications. There remains a lack of published research regarding risk factors for enteric leaks.

Methods: As such we undertook a retrospective cohort study of SPK transplants performed at Westmead Hospital over twenty years (between 1998-2017, n=425) to identify the occurrence of enteric leaks as well as donor, recipient and transplantation procedure risk factors. Descriptive statistics were generated using SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). The student's t-test and/or Mann-Whitney U test was used to detect significance. All tests were two tailed and any statistically significant difference was considered at the P <0.05 level.

Results: Of the 425 patients, 16 (3.5%) experienced an enteric leak. Of these, 12 (80%) had significant vascular disease, defined as coronary artery disease, cerebrovascular disease, retinopathy, peripheral neuropathy or peripheral vascular disease requiring surgical intervention. The risk of an enteric leak increased in recipients with significant vascular disease.

Conclusion: The rates at Westmead Hospital were lower than those published in the literature. We demonstrated that the presence of significant vascular disease predisposed recipients to enteric leak. These findings highlight the importance of careful donor and recipient selection to optimise patient outcomes.

Introduction

Decades of treatment of patients with Simultaneous Pancreas-Kidney (SPK) transplantation has demonstrated its utility as the most optimal form of treatment of patients suffering from type 1 diabetes mellitus and end-stage renal failure as it uniquely treats renal failure whilst restoring normoglycaemia [1-4]. SPK transplantation is the most common pancreas transplant modality, accounting for 75% of pancreas transplants performed worldwide [5]. The technique of choice for handling the exocrine component has become enteric drainage of the pancreatic exocrine secretions [1, 6-9]. This is because it facilitates the better physiological handling of the exocrine secretions than the

[*]*Correspondence to: Henry Pleass, Ph.D., Department of Surgery, Westmead Hospital, Westmead Clinical School, The University of Sydney, Westmead, 2145, New South Wales, Australia; Tel: 61288907365; Fax: 61296339351; E-mail: henry.pleass@sydney.edu.au*

http://dx.doi.org/10.31487/j.JDMC.2020.02.02

traditional technique of bladder drainage. It avoids the potential complications of severe reflux pancreatitis, hyperchloremic metabolic acidosis and dehydration due to loss of the alkaline pancreatic secretions. Rather more importantly, it also avoids the typically seen urologic complications of infection, urethritis, severe cystitis and haematuria that are associated with the previously favoured bladder drainage technique

Over the last three decades, global five-year patient and graft survival rates have improved to 85% and 75% respectively and the estimated half-life of a pancreatic graft has increased to 14 years [1, 10]. This improvement is multifactorial, contributed to by changes in surgical technique, and other factors including changes in immunosuppressive regimen, organ donor preservation solutions, anaesthesia, ICU care, donor and recipient selection and more accurate diagnosis of rejection [1, 3, 4, 11].

Despite its long-term success, it remains a technically challenging procedure, associated with the highest complication rate of all solid organ transplantation [1-4, 12, 13]. One particularly challenging complication of this procedure is that of enteric leaks of the duodenal stump that can result in focal and systemic infection and, ultimately, loss of the pancreas graft [1, 14, 15]. Some controversies exist as to what is defined as high or low incidence, with a range observed in the literature between 5-10% [1-4, 12, 13]. The majority of enteric leaks occur early in the post-operative period and are most likely due to technical complications, such as ischaemia of the duodenal stump from the donor and technical issues in donor surgery or back table dissection [2, 16]. Additional contributing factors can include the intense immunosuppressive regime used, acute cellular rejection or presence of infections around the pancreas [2, 17]. Alternatively, delayed leaks are more often related to the duodenal stump closures, with previous evidence demonstrating that chronic ischaemia could be a contributing factor [18]. The majority of the literature on duodenal stump leaks after pancreas transplantation has predominantly focused on duodenocystostomies, as for the first decades of SPK, they were preferred rather than duodenoenterostomies; the latter of which has become the current technique of choice [1]. As such there remains a lack of published research exploring potential risk factors contributing to enteric leaks and means for preventing such.

The purpose of this study was to explore the rate of enteric leaks in a previously never done before large population of SPK recipients and to identify underlying risk factors. Also, specifically, to evaluate how donor and recipient co-factors contributed to enteric leaks and to provide guidance as to the best options for choice of donor, recipient and surgical techniques in order to minimise enteric leaks and loss of the pancreas transplant.

Materials and Methods

I Study Population

All pancreas transplants at Westmead Hospital performed between January 1998 and December 2017 ($n = 425$) were collected from medical records, including both hardcopy files and electronic medical records on the 2011 Cerner Millennium PowerChart software, where available. Information was analysed to identify enteric leaks that occurred at any stage post-operatively. Both SPK and PAK procedures were included in the database and organ recipients had at least twelve months follow-up after transplantation.

II Surgical Procedure

All organ donor retrieval procedures were performed by a surgical team including a Consultant surgeon and according to our previously published standard protocol [19, 20]. Organ allocation was based on recipient-to-donor ABO compatibility, negative cytotoxic cross match testing and wait time.

As per our previously described surgical method, the pancreas transplants were performed with systemic venous drainage and, in the majority or 84%, enteric drainage of the exocrine pancreas was employed [9, 19, 21]. In the remaining 16%, bladder drainage of the exocrine pancreas was utilised, these were used as a comparator group. University of Wisconsin organ preservation solution was used for all donor organ perfusion. The portal vein of the pancreatic allograft was anastomosed to the recipient's external iliac vein. In almost all cases, a standard venous extension graft was utilised and an arterial extension, or "Y-graft", anastomosed to the recipient's common iliac artery was used wherever possible.

More specifically regarding the duodenoenterostomy, once the pancreatic graft was re-perfused, the recipient's proximal jejunum was identified, and an appropriate site selected for the tension-free anastomosis to the graft duodenum [21]. A 2-3cm enteroenterostomy was routinely fashioned, the donor duodenal segment rinsed thoroughly with 0.5% aqueous chlorhexidine, prior to a hand sutured two layered anastomosis with 3-0 PDS [21]. This enteric anastomosis was created away from the medial duodenal staple line, to avoid the potentially most ischaemic area of the duodenum. Regarding the vascular supply of the duodenum, the gastroduodenal artery was never reconstructed, instead tied off. This technique was employed in the majority of cases, although a smaller number underwent a bladder drained technique, again using two layers of 3-0 PDS, onto the bladder dome. A further small cohort had a stapled enteric anastomosis using a liner cutting stapler, with the stapler defect closed with 3-0 PDS continuous suture.

Immunosuppression from 2001 was provided using basiliximab on days 0 and 4, followed by tacrolimus, mycophenolate mofetil and prednisolone in all cases, which is the standard protocol at our institution. Prior to 2001 the regimen used was cyclosporine, mycophenolate mofetil and prednisolone.

III Identification of Enteric Leaks

In all patients, clinical symptoms of acute peritonitis, such as fever, abdominal pain, general malaise, purulent wound discharge, ileus, diarrhoea, nausea, vomiting, acute abdomen and sepsis, led to either investigation via computed tomography (CT) scanning, or an immediate laparotomy. If free gas or retained fluid was noted around the pancreas on CT scanning, and an enteric leak was suspected, an explorative laparotomy was undertaken. If a leak was confirmed and the pancreas could be preserved, the affected duodenal segment was mobilised the previous anastomosis site resected and conversion to bladder-drainage was performed with prolonged decompression of the bladder using an indwelling catheter.

Time until leak was defined as days from transplantation until diagnostic confirmation of enteric leak [1]. Clinical findings and management were analysed retrospectively.

IV Risk Factors

Risk factors for enteric leaks were collected and analysed. These included donor factors of:

i. Age – in years.
ii. Gender – if the patient was biologically male or female.
iii. BMI – weight in kilograms over height in meters squared.
iv. Hypertension – If the patient had an elevated systolic blood pressure and was receiving treatment with anti-hypertensive medications.
v. Smoking status – If the patient was a current smoker, previously smoked or had never smoked.
vi. Significant vascular disease – If the patient had cardiac vascular disease (a previous myocardial infarction, coronary artery bypass or angioplasty), cerebral vascular disease (a previous stroke or transient ischaemic attack), evidence of micro-vascular disease (retinopathy or neuropathy) and evidence of significant peripheral vascular disease that required operative intervention (arterial bypass and/or extremity amputation). It did not include patients that solely had peripheral vascular disease or only had evidence of macro-vascular disease (iliac artery calcification or aortic calcification) as these were present in the majority of patients in the cohort.
vii. Cause of death and donor pathway – if the pancreas was donated from a brain-dead donor (DBD) or a circulatory death donor (DCD).

Recipient factors analysed included: age, gender, BMI, hypertension, smoking status, and significant vascular disease as defined previously. An additional risk factor considered was the lowest blood pressure of the recipient over the duration of the transplant operation and 24 hours post-operatively.

Transplantation procedure characteristics included:

i. Intra-operative hypotension – If the systolic blood pressure was noted to be <90 mmHg during the operation by the anaesthetic team.
ii. Fluid boluses – If the recipient required a fluid bolus during the operation to treat hypotension and prevent possible associated complications.
iii. Vasopressor use – If intra-operative vasopressors were used to maintain blood pressure and perfusion of the graft during the procedure.
iv. Antibiotics administered – Which antibiotics were given during the transplantation procedure.
v. Cold ischaemic time – The time from when the organ was perfused during the retrieval procedure until it was removed from ice and the anastomosis was performed.
vi. Anastomotic time – The time taken to anastomose the graft to iliac vessels.
vii. Venous graft – If an extension graft was used or not.
viii. Arterial graft – Y shaped arterial extension graft formed using the donor common iliac artery bifurcation.
ix. The kidney donor profile index (KPDI) – a score of 1-100% allocated to the transplanted kidney that indicates the percentage relative risk of failure.

The renal delayed graft function, further classified as:

i. Category 1 – immediate function with a spontaneous fall in creatinine of ≥10% in the first 24 hours post-transplant.
ii. Category 2 – delayed immediate function with a spontaneous fall in creatinine of ≥10% in the first 25-72 hours post-transplant.
iii. Category 3 – poor immediate function with no spontaneous fall in creatinine at 72 hours post-transplant but no dialysis required.
iv. Category 4 – no immediate function with no spontaneous fall in serum creatinine and dialysis required within 72 hours post-transplant.

V Follow-Up

The recipients' admissions were screened for a minimum of six months following transplantation. Pancreatic graft loss was defined as return to insulin dependency or having the graft removed or relisted onto the transplant waitlist [1, 7]. Acute rejection was defined as severe rejection after a period of normal graft function; subacute rejection as progressive or repeated moderate-severe rejection; and chronic rejection as a slow, progressive deterioration in graft function after months of stable function. The era effect for the years prior to 2013 versus the years following and including 2013 was reviewed ($p = 0.94$).

VI Statistical Analysis

The study cohort was analysed using descriptive statistics generated using SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Continuous data are presented with means ± standard deviations or medians with interquartile range (25th to 75th percentile). The student's t-test or Mann-Whitney U test was used to detect significance. All tests were two tailed and any significant difference was detected at the $P < 0.05$ level.

Results

I Demographics

Four hundred and twenty-five patients underwent pancreas transplantation at our institution over the 20-year period. Of these, 358 (84.2%) were enteric drained and 67 (15.8%) were bladder drained with 406 (95.5%) being SPK procedures. Of the enteric drained pancreatic transplants, 338 (93.3%) were performed using the hand sewn anastomosis technique and 20 (5.60%) using the stapled technique described in section 2.2. Additionally, 13 procedures (3.0%) were PAK following graft loss and 6 (1.4%) were pancreas transplant alone, none of which experienced an enteric leak. Of the pancreas grafts, nine (2.10%) were recovered from DCD donors with the remaining 416 (97.9%) being from DBD donors; consistent with current rates in the literature [1]. As demonstrated in (Table 1), the mean donor age was 26.86 ± 0.9 for those without an enteric leak and 33.0 ± 2.6 for those with an enteric leak. The median recipient age was 24.6 ± 1.9 and 18.0 ± 6.8 respectively. The mean cold ischaemic ($P = 0.09$), warm ischaemic ($P = 0.12$) and anastomotic times ($P = 0.06$) were similar between the groups.

Of the 425 recipients, 16 (3.8%) experienced an enteric leak. These all occurred in patients with an enterically drained pancreas transplant performed using the hand sewn anastomotic technique. Of the 16 enteric leaks, 12 (75%) occurred early (median 13 days; IQR 10-13 days) and 4 (25%) occurred late (median 51 days, IQR 36-65 days). All 16 enteric leaks occurred from the duodenal staple line, distant from the enteric anastomosis. All 16 patients were returned to theatre and converted to bladder drainage with the graft salvaged in all but one case. There was no association observed between leak volume output and outcomes. At time of publication, one recipient had experienced graft failure secondary to a chronic enteric leak and sepsis, which required a graft pancreatectomy on day 35 post-transplantation. Additionally, two recipients experienced graft loss secondary to chronic graft rejection approximately three years after their enteric leaks occurred. One recipient experienced graft loss secondary to thrombosis on day 50 post transplantation, after having an enteric leak on 16 and another on day 358 after experiencing an enteric leak on day 13.

Table 1: Donor, Recipient, and Intra-operative Factors.

Variable	Without EL (n, (%))	With EL (n, (%))	P values
Donor			
Male	62 (50.8)	10 (62.5)	0.68
Female	60 (49.2)	6 (37.5)	0.68
Mean Age ± SD (years)	26.86 ± 0.9	33.00 ± 2.6	0.24
Donors after Brain Death	416 (97.9)	16 (100)	0.18
Donors after Cardiac Death	9 (2.1)	0 (0.0)	0.18
Current Smoker	11 (84.6)	2 (15.4)	0.16
Former Smoker	5 (100)	0 (0.0)	0.16
Non-Smoker	102 (96.2)	4 (3.8)	0.16
Mean BMI ± SD	20.7 ± 0.8	22.6 ± 3.4	0.55
Delayed renal graft function category 2	13.0 (3.1)	3 (18.8)	0.32
Delayed renal graft function category 3	13.0 (3.1)	1 (6.3)	0.24
No immediate renal graft function	3 (0.7%)	0 (0.0)	0.18
Recipient			
Male	228 (57.1)	12 (75.0)	0.16
Female	171 (44.0%)	4 (25.0)	0.16
Mean Age ± SD (years)	24.6 ± 1.9	18.0 ± 6.8	0.49
Current Smoker	11 (84.6)	2 (12.5)	0.08
Former Smoker	120 (29.0)	8 (50.0)	0.08
Non-Smoker	146 (96.7)	6 (37.5)	0.08
Mean BMI ± SD	24.2 ± 0.6	26.3 ± 1.8	0.33
Hypertension	277 (67.0)	13 (81.3)	0.16
Diabetes	5 (100)	0 (0.00)	1.00
Significant Vascular Disease	119 (97.5)	12 (75.0)	0.01
Intra-operative Factors			
Mean cold ischaemia time ± SD (min)	30.1 ± 1.1	36.9 ± 4.2	0.09
Mean warm ischaemia time ± SD (min)	0.3 ± 0.05	0.0 ± 0.0	0.12
Mean total ischaemic time (min) ± SD	30.2 ± 1.1	37.9 ± 4.4	0.07
Mean pancreas anastomotic time (min) ± SD	27.13 ± 0.4	30.60 ± 3.3	0.06
Intraoperative pressors required	85 (91.4)	8 (8.6)	0.68
Intraoperative fluid bolus required	43 (84.3)	8 (15.7)	0.01
Venous graft	62 (92.5)	5 (7.5)	0.77
Arterial graft	108 (91.5)	10 (8.5)	1.00
Post-operative Factors			
Lowest BP ± SD (mmHG)	95.36 ± 2.93	90.47 ± 9.94	0.59
Time to postoperative EL (days)	N/A	29.00 ± 11.26 (Median 13.00 days (*IQR* = 11.50–30.25))	

II Risk Factors

As demonstrated in (Table 1), 12 (75.0%) of the recipients who experienced an enteric leak had significant vascular disease or a history of cardiac vascular disease (a previous myocardial infarction, coronary artery bypass or angioplasty), cerebral vascular disease (a previous stroke or transient ischaemic attack), evidence of micro-vascular disease (retinopathy or neuropathy) and evidence of significant peripheral vascular disease that required operative intervention (arterial bypass and/or extremity amputation). Additionally, eight (50.0%) recipients were former smokers and two (12.5%) recipients were current smokers. Four (25.0%) of the donor renal grafts experienced delayed graft

function. More specifically, three of these were classified as poor immediate function, or category three, and one with delayed immediate function, or category two.

The results showed a significant association in recipients with significant vascular disease with the risk of enteric leaks compared to those without significant vascular disease (p = 0.01). The requirement of an intraoperative fluid bolus was also significantly associated with the risk of an enteric leak (p = 0.01). There were no significant differences observed regarding donor gender, age smoking status, mechanism of death, mean BMI or delayed graft function. Additionally, there were no significant differences regarding recipient gender, age, smoking status, mean BMI presence of hypertension or diabetes or regarding the other intra-operative risk factors. The KDPIs were only recorded from July 2017 and, therefore, provided insufficient numbers for analysis.

Discussion

Outcomes of SPK transplants have improved over the past decade, which is reflected in this study with one-year graft and patient survival rates both being 81% and 99% respectively [1]. Additionally, the five-year graft and patient survival rates are 73.9% and 96% respectively, with the majority of graft losses being secondary to thrombosis. Recent research has demonstrated that the rates of enteric leaks following pancreatic transplantation may have decreased, mainly due to improvements in surgical technique [1, 3, 11, 13, 22]. Other contributing factors include improvements in immunosuppressive regimen, preservation solutions, anaesthesia, ICU care, donor and recipient selection and more accurate diagnosis of rejection [3, 4].

However, pancreas transplants remain associated with the highest surgical complication rates, with multiple studies demonstrating the rates of enteric leaks are between 5-10% [1-4, 6, 13, 14]. Previous research conducted at our institution on a smaller population and shorter time frame noted an incidence of 1.2% [9]. Interestingly, the findings in this study also reflected an improvement on this literature over a longer time period, with enteric leaks occurring in or 3.8% of the patient population, potentially reflecting a change in donor and recipient demographics over time and supporting our unique findings. All leaks in this series were from the blind end of the stapled duodenum and not from the hand sewn or stapled enteric anastomosis. Duodenal staple lines were routinely buried using a 3-0 PDS suture, although concern remains that this may further compromise the seromuscular layer of the graft duodenum in the fluid overloaded post-operative state.

Although not analysed in this review, factors that have previously been suggested to contribute to the early leaks include the donor duodenum experiencing reperfusion oedema, ischaemic damage or colonisation with pathogenic bacteria, impaired wound healing secondary to the immunosuppressive regimen or technical complications [2, 4]. On the other hand, late enteric leaks are more likely to have been caused by infection, rejection or ischaemia [4]. Recipient significant vascular disease, which could increase the risk of the above occurring, has been shown to significantly decrease pancreas graft survival rates, with research from as early as the 1990s recommending significant vascular disease to be a potential exclusion criteria [15, 16]. Interestingly, in this study, recipient significant vascular disease was found to have a statistically significant association with enteric leaks (p = 0.01). This may be a novel explanation for the occurrence of enteric leaks and indicates an area for further research.

It is estimated that more than one third of pancreatic transplant recipients are aged over 45 years of age 22. Despite this, it has been suggested that survival rates are significantly higher for recipients under the age of 45, with those over 45 years having significantly increased risk of morbidity, including enteric leaks and graft loss, and mortality [4, 6, 7, 16, 23, 24]. Our study supported this by demonstrating an association between increased age and rates of enteric leaks. Interestingly, our national protocol does not exclude patients on the basis of age alone and selective patients are still transplanted over the age of 50.

Additionally, obesity is associated with an increased risk of post-transplant graft loss, technical failures, including enteric leaks and patient mortality [6, 23, 25-27]. This study demonstrated a weak association between obesity and an increased risk of enteric leaks. Despite the weak association observed between male gender and enteric leaks, there remains a lack of similar published findings, with other studies observing no significant difference in complication rates between genders [1, 23, 27].

Despite smoking being a contraindication to pancreas transplantation at our institution, 19 patients in the cohort admitted to ongoing smoking during their anaesthetic assessment, with two of these experiencing enteric leaks. Moreover, half of those who experienced an enteric leak were ex-smokers. Therefore, this could be something treating doctors consider when assessing patients for pancreatic transplantation.

These findings have identified potential risk factors for enteric leaks and screening considerations that should be used when selecting donors and recipients to help prevent significant morbidity and mortality outcomes. Whilst we recognise that these findings are not statistically significant, they hold clinical significance. Novel research at our institution has demonstrated that donors aged 35 to 45 years of age and those that are obese have a significant increased risk of thrombosis resulting in graft failure, supporting the associations demonstrated in this study. Therefore, there exists scope for careful donor and recipient selection to ensure the best outcomes for patients, including decreased re-laparotomy rates, length of stay and healthcare costs.

Strengths and Limitations

Strengths of this study included the surgical technique used, as 358 (84.2%) of SPK procedures were performed using enteric drainage to handle the exocrine component, which is associated with higher patient and graft survival rates than bladder drainage [7, 11]. In the series of enteric leaks that underwent re-laparotomy, no damage to the Y-graft was noted and in the majority of cases the reperfusion was observed to be ‘excellent’, ‘good’ or ‘satisfactory’. Finally, the blind end of the graft duodenum was stapled, which is an easy and quick procedure with low complication rates [28]. It was then oversewn with 3-0 PDS, to bury the staple line, and was not incorporated into the enteric anastomosis. The use of hand sewing has also been supported in the literature with lower rates of post-operative bleeding and higher graft survival rates observed compared to stapling alone [5]. Therefore, combining these techniques could be responsible for the improved outcomes, although oversewing the staple lines may cause injury to the graft duodenum, rather than being

protective. Fluid overload in the peri-operative period could well be a contributing factor in enteric leaks and warrants a prospective trial of fluid management.

Furthermore, all enteric anastomoses were technically positioned so that a salvage duodenovesical anastomosis could be created. Transplantation units often position the head and duodenum of the pancreas graft cranially in order to simplify the anastomosis, which potentially limits their options in regard to converting to bladder drainage [29]. At our institution, the head of the pancreas is placed towards the bladder, facilitating conversion to bladder drainage and decompression of the system should an enteric leak occur. There exists minimal analysis of this technique in the literature, with Sollinger *et al.* being one of the few institutions who examined over 1,000 SPKs at their institution with a combination of cranial and caudal placements used. Their rate of enteric leaks was slightly higher at 5.7% over the 22-year period, however their complication rates were similar to ours [6].

The key limitation to this study is the limited sample size. The number of pancreas transplants performed over the 20-year period studied was restricted by availability of the organs and only a single institution was studied. Therefore, the enteric leaks observed were small in number, limiting the power of the study and possible conclusions, particularly strongly identifying key risk factors and the time-dependant development of leaks. Additionally, it was a single centre study and there was no comparison regarding the different drainage methods for the pancreatic secretions, namely enteric drainage compared to bladder drainage, as our institution primarily performed SPK transplants utilising the enteric drainage technique during this time period. To compensate for these limitations, our centre followed a standard protocol over the study period.

Conclusion

At Westmead in our patient cohort over the past 20-years, the rate of enteric leaks has been significantly lower than what has previously been reported. When controlling for all variables, we found there was an association between significant vascular disease and enteric leaks. Therefore, it is clear that meticulous donor and recipient surgical technique are crucial to limit this morbid complication, as well as consideration for reduction in peri-operative fluid overload, causing further tension on the graft duodenum. Abstinence from cigarette smoking and or no prior history of smoking is also associated with a reduced risk of enteric leaks in the post-operative period. These findings clearly highlight the potential risk factors for enteric leaks and that further research in this area is required. By far the most important factor affecting outcomes is that of careful donor and recipient selection. Critical evaluation of the donor selection process should include focusing on donors that have no history of smoking, should be from the younger age groups and of a healthy weight. These would appear to be imperative to ensure best graft and patient outcomes.

Abbreviations

BMI: Body Mass Index
CT: Computed Tomography
DBD: Donor after Brain Death
DCD: Donor after Circulatory Death
KDPI: Kidney Donor Profile Index
PAK: Pancreas After Kidney
SPK: Simultaneous Pancreas Kidney

Author Contributions

A.H: Designed Research, Literature Review, Data Collection, Wrote and Edited Paper; S.S: Analysed Data, Edited Paper; K.H: Analysed Data, Edited Paper; P.R: Assisted with Data Collection, Edited Paper; K.K: Assisted with Data Collection; A.W: Edited Paper; G.W: Edited Paper; N.R: Edited Paper; P.O: Edited Paper; B.N: Edited Paper; J.C: Edited Paper; W.J.H: Participated in article content writing, revision and editing; H.C.P: Supervised project and Edited Paper.

Ethical Approval

Ethics approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee, approval number SAC2014/12/6.15(4188) QA.

Conflicts of Interest

None.

Funding

None.

REFERENCES

1. Vinzent N Spetzler, Nicolas Goldaracena, Max A Marquez, Sunita K Singh, Andrea Norgate et al. (2015) Duodenal leaks after pancreas transplantation with enteric drainage - characteristics and risk factors. *Transpl Int* 28: 720-728. [Crossref]
2. Dilip S Nath, Angelika Gruessner, Raja Kandaswamy, Rainer W Gruessner, David Er Sutherland et al. (2005) Late anastomotic leaks in pancreas transplant recipients - clinical characteristics and predisposing factors. *Clin Transplant* 19: 220-224. [Crossref]
3. G B Zibari, D F Aultman, K D Abreo, M L Lynn, E Gonzalez et al. (2000) Roux-en-Y venting jejunostomy in pancreatic transplantation: a novel approach to monitor rejection and prevent anastomotic leak. *Clin Transplant* 14: 380-385. [Crossref]
4. R W Gruessner, D E Sutherland, C Troppmann, E Benedetti, N Hakim et al. (1997) The surgical risk of pancreas transplantation in the cyclosporine era: an overview. *J Am Coll Surg* 185: 128-144. [Crossref]
5. J P Lindahl, R Horneland, E Nordheim, A Hartmann, E M Aandahl et al. (2018) Outcomes in Pancreas Transplantation With Exocrine Drainage Through a Duodenoduodenostomy Versus Duodenojejunostomy. *Am J Transplant* 18: 154-162. [Crossref]
6. Hans W Sollinger, Jon S Odorico, Yolanda T Becker, Anthony M D'Alessandro, John D Pirsch (2009) One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg* 250: 618-630. [Crossref]
7. Angelika C Gruessner, Rainer W G Gruessner (2016) Pancreas Transplantation of US and Non-US Cases from 2005 to 2014 as Reported to the United Network for Organ Sharing (UNOS) and the

International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 13: 35-58. [Crossref]

8. Chandana G Lall, Kumaresan Sandrasegaran, Dean T Maglinte, Jonathan A Fridell (2006) Bowel complications seen on CT after pancreas transplantation with enteric drainage. *AJR Am J Roentgenol* 187: 1288-1295. [Crossref]
9. Thwaites S.E L, V.W.T, Yao J, Kable K, Jenkins L, Chen C, Robertson P, Hawthornw W.J, Ryan B.J, Pleass H.C, Allen, R.D.M (2012) Surgical Morbidity of Simultaneous Kidney and Pancreas Transplantation: A Single-Centre Experience in the Tacrolimus Era. *ISRN Transplantation* 2013.
10. Rainer W G Gruessner, Angelika C Gruessner (2013) The current state of pancreas transplantation. *Nat Rev Endocrinol* 9: 555-562. [Crossref]
11. Eric J Siskind, Leo I Amodu, Sonia Pinto, Meredith Akerman, Johann Jonsson et al. (2018) Bladder Versus Enteric Drainage of Exocrine Secretions in Pancreas Transplantation: A Retrospective Analysis of the United Network for Organ Sharing Database. *Pancreas* 47: 625-630.
12. J Quintela, J Aguirrezabalaga, A Alonso, C Fernandez, G Corbal et al. (2009) Portal and systemic venous drainage in pancreas and kidney-pancreas transplantation: early surgical complications and outcomes. *Transplant Proc* 41: 2460-2462. [Crossref]
13. Mathieu Page, Thomas Rimmelé, Charles-Eric Ber, Françoise Christin, Lionel Badet et al. (2012) Early relaparotomy after simultaneous pancreas-kidney transplantation. *Transplantation* 94: 159-164. [Crossref]
14. A Manrique, C Jiménez, R M López, F Cambra, J M Morales et al. (2009) Relaparotomy after pancreas transplantation: causes and outcomes. *Transplant Proc* 41: 2472-2474. [Crossref]
15. H W Sollinger, J S Odorico, S J Knechtle, A M D'Alessandro, M Kalayoglu et al. (1998) Experience with 500 simultaneous pancreas-kidney transplants. *Ann Surg* 228: 284-296. [Crossref]
16. David E R Sutherland, Rainer W G Gruessner, David L Dunn, Arthur J Matas, Abhinav Humar et al. (2001) Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 233: 463-501. [Crossref]
17. E N Heredia, M J Ricart, E Astudillo, M Lopez Boado, S Delgad et al. (2002) Pancreas transplantation with enteric drainage: duodenal segment leak. *Transplant Proc* 34: 215. [Crossref]
18. T Nymann, M H Shokouh Amiri, D S Elmer, R J Stratta, A O Gaber (1997) Diagnosis, management, and outcome of late duodenal complications in portal-enteric pancreas transplantation: case reports. *J Am Coll Surg* 185: 560-566. [Crossref]
19. Ahmer Hameed, Teresa Yu, Lawrence Yuen, Vincent Lam, Brendan Ryan et al. (2016) Use of the harmonic scalpel in cold phase recovery of the pancreas for transplantation: the westmead technique. *Transpl Int* 29: 636-638. [Crossref]
20. Hawthorne WJP, H.C. Hameed, A. (2018) Pancreas Retrieval for Whole Organ and Islet Cell Transplantation. *Organ Donation and Transplantation*. United Kingdom: Intech Open Limited 2018: 153-186.
21. Vincent W T Lam, Kit Wong, Wayne Hawthorne, Brendan Ryan, Howard Lau et al. (2006) The linear cutting stapler for enteric anastomosis: a new technique in pancreas transplantation. *Transpl Int* 19: 915-918. [Crossref]
22. Angelika C Gruessner (2011) 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 8: 6-16. [Crossref]
23. E B Finger, D M Radosevich, T B Dunn, S Chinnakotla, D E R Sutherland et al. (2013) A composite risk model for predicting technical failure in pancreas transplantation. *Am J Transplant* 13: 1840-1849. [Crossref]
24. Robert Ollinger, Christian Margreiter, Claudia Bösmüller, Annemarie Weissenbacher, Florian Frank et al. (2012) Evolution of pancreas transplantation: long-term results and perspectives from a high-volume center. *Ann Surg* 256: 780-786. [Crossref]
25. Marcelo Santos Sampaio, Pavani Naini Reddy, Hung Tien Kuo, Neda Poommipanit, Yong Won Cho et al. (2010) Obesity was associated with inferior outcomes in simultaneous pancreas kidney transplant. *Transplantation* 89: 1117-1125. [Crossref]
26. Rajinder Pal Singh, Georgios Vrakas, Samiha Hayek, Sara Hayek, Sadia Anam et al. (2013) Clinically significant peripancreatic fluid collections after simultaneous pancreas-kidney transplantation. *Transplantation* 95: 1263-1269. [Crossref]
27. Abhinav Humar, Thigarajan Ramcharan, Raja Kandaswamy, Rainer W G Gruessner, Angelika C Gruessner et al. (2004) Technical failures after pancreas transplants: why grafts fail and the risk factors--a multivariate analysis. *Transplantation* 78: 1188-1192. [Crossref]
28. Jonathan A Fridell, Martin L Milgrom, Sharon Henson, Mark D Pescovitz (2004) Use of the end-to-end anastomotic circular stapler for creation of the duodenoenterostomy for enteric drainage of the pancreas allograft [corrected]. *J Am Coll Surg* 198: 495-497. [Crossref]
29. Hany El Hennawy, Robert J Stratta, Fowler Smith (2016) Exocrine drainage in vascularized pancreas transplantation in the new millennium. *World J Transplant* 6: 255-271. [Crossref]