Immunotherapy and beta-cell replacement in type I diabetes mellitus

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Chapter 6

Pancreas Transplantation: advantages of both enteric and bladder drainage combined in a two-step approach

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ABSTRACT

Although there is a tendency to perform enteric drainage of pancreas transplants in simultaneous pancreas-kidney (SPK) transplantation, bladder drainage is still preferable in pancreas transplantation alone (PTA) or after a previous kidney transplantation (PAK). Our hypothesis was that enteric conversion of a bladder drained pancreas is an effective and safe procedure. We studied the complication rate and physiological effects of enteric conversion in patients with primary bladder-drained SPK transplantation.

We performed 51 enteric conversions in bladder-drained SPK transplant recipients. As we observed a low complication rate, with time enteric conversions were also performed for less strict and severe indications.

The main indications for conversion were urological problems, metabolic complications and reflux-pancreatitis. The median transplantation-conversion interval was 12 months (range 2-40 months). Post-operative complications consisted of seven urinary tract infections, two low-grade superficial wound infections, one minor bleeding, one phlebitis and one paralytic ileus. In two patients, a relaparotomy was necessary. No graft rejection following enteric conversion was found. Long-term renal and pancreatic function were not affected by the enteric conversion. Three-year patient, kidney and pancreas survival rates after enteric conversion were 93%, 97%, and 93%, respectively (censored data).

Enteric conversion after pancreas transplantation is an effective and safe procedure. Therefore, we suggest a policy of a two-step approach of primary bladder drainage followed by an enteric conversion of the pancreas in a selected group of SPK patients.

INTRODUCTION

Simultaneous pancreas-kidney (SPK) transplantation is an established therapeutic option in patients with type I diabetes mellitus and end-stage renal failure (1-6). The management of the exocrine drainage of the pancreatic graft has been a matter of debate for years. For decades, bladder drainage was the most common method of duct management (7). This type of duct management was introduced to decrease the incidence of diffuse abdominal infections and to monitor for pancreas rejection following urine amylase and lipase levels. Now a tendency towards a more physiological enteric drainage is seen (7). Both bladder and enteric drainage procedures have their own particular complications. The main disadvantages of bladder drainage are long-term complications like urinary tract infections, haematuria, dehydration, metabolic acidosis and reflux-pancreatitis (1,8,9). Concerning the enteric drainage procedure, several reports demonstrated significantly higher intra-abdominal infection rates and lower pancreas graft survival than that of bladder-drained transplants (2,10-13). The International Pancreas Transplant Registry demonstrated slightly higher (but not significant) pancreas graft survival rates in bladder-drained vs. enteric-drained transplants, especially in the solitary pancreas transplantation groups (7). With a two-step approach of primary bladder drainage followed by an enteric conversion, short-term disadvantages of primary enteric drainage and the long-term bladder drainage-related complications may be prevented. Previous studies already described the therapeutic relevance and possible disadvantages of enteric conversion. After enteric conversion, surgical reintervention occurred in 24% of the patients. The most common surgical complication was leakage of the anastomosis (8.4% of all patients) (14). With prednisone, cyclosporin and azathioprine as maintenance immunosuppression in the SPK group in 13% of the patients, rejection treatment was given after conversion (8). In the pancreas transplantation alone (PTA) group, even 55% needed anti-rejection treatment, which led to graft loss in 64% of these recipients. Immunologic graft loss was highest for recipients of pancreas transplants alone, who underwent conversion within six months after transplantation or within one year after their last rejection episode (8).

Historically, in our institution, bladder drainage was the procedure of choice. With this technique, excellent survival rates were obtained (5,6). Owing to long-term urological and metabolic complications, enteric conversion was performed in a number of patients. As we observed a low complication rate, enteric conversions were also performed for less strict and severe indications. With this two-step approach, we prevented the short-term disadvantages of primary enteric drainage and the long-term bladder drainage-related complications. In the present study, we investigated the time interval between transplantation and conversion, length of hospital stay, complication rate, graft function, rejection rates and survival rates in 51 patients with SPK with primary bladder drainage

after enteric conversion in the current immunosuppressive era. Our hypothesis was that enteric conversion of the pancreas is an effective and safe procedure .

MATERIALS AND METHODS

Between October 1996 and April 2003, 51 enteric conversions of the pancreas graft were performed in patients with SPK and primary bladder drainage. Follow-up of these patients ended in April 2004. Immunosuppressive treatment consisted of mycophenolate mofetil, cyclosporin and prednisone. Twenty patients (39.2%) had no induction treatment and 31 patients (60.8%) received anti-thymocyte globulin or daclizumab. Rejection episodes occurred in 58.8% of the patients.

When enteric conversion of the pancreas graft was performed, the duodenocystostomy was isolated and devided. Subsequently, the cystostomy was closed in two layers, using a running absorbable PDS 4/0 (Ethicon, Somerville, NJ, USA) suture. A side-to-side duodeno-enterostomy was performed between the graft duodenum and the ileum, using a two-layer approach with a PDS 4/0 (Ethicon) running suture. An urethral catheter was left in place for 5 days. Profylactic intravenous antibiotics were given for 24 hours: benzylpenicilin $1x10^6$ U four times per day, ceftazolin 1000 mg three times per day, gentamicin 1.5 mg/kg once per day and metronidazol 500 mg three times per day. Oral feeding was started as soon as possible.

We analyzed the indication for enteric conversion, transplantation-conversion interval, length of hospital stay, surgical complications, resolution of symptoms and rejection and survival rates. Furthermore, changes in sodium bicarbonate use, urinary protein and sodium loss, number of antihypertensive drugs, pancreatic endocrine function (HbA1c) and renal clearance (Nankivell method) in the 6 months before and after conversion were analysed. Patients using co-trimoxazol as prophylactic treatment in the period preceding to the conversion were excluded when renal clearance was analyzed, because of its effect on serum creatinin levels (15). Graft loss of the pancreas was defined as exogenous insulin dependence and graft loss of the kidney as starting of dialysis. Patient death with functioning graft was not considered as graft loss. Patient survival rate was calculated until April 1st 2004. The median follow up after conversion was 36 months.

Statistical analysis was performed using the Paired Samples t-test (two-tailed). If criteria for this test were not met, the Wilcoxon signed-ranks test was used.

RESULTS

In 51 patients with SPK and primary bladder drainage, an enteric conversion was performed. Indications for enteric conversion were urinary tract-related problems (n=39), excessive sodium bicarbonate loss with hypotensive periods (n=3), need for large amounts of oral sodium bicarbonate intake (n=20), reflux-pancreatitis (n=2) and suspicion on a vesico-cutaneous fistula (n=1). In 12 patients there was more than one indication (Table 1).

Table 1: Indications for enteric conversion in 51 patients*

Indication	Number
Recurrent cystitis	15
Haematuria	9
Bladder dysfunction	7
Dysuria	4
Pyelonephritis	2
Urethritis	1
Prostatitis	1
Discomfort of oral $NaHCO_3$ intake	20
Excessive $NaHCO_3$ and hypotension	3
Reflux-pancreatitis	2
Suspicion of vesico-cutaneous fistula	1

* in 12 patients there was more than one indication

The median transplantation-conversion interval was 12 months (range 2 to 40 months). The median length of hospital stay was 9 days (range 6 to 57 days).

Post-operative complications are summarized in Table 2. There were two low-grade superficial wound infections (4%), seven urinary tract infections (14%), one paralytic ileus, one phlebitis and one minor bleeding without necessity of surgical reintervention (2%). Two relaparotomies (4%) were performed. One patient developed abdominal pain with fever. Drain fluid consisted high levels of amylase. Owing to these symptoms and signs, an anastomotic leakage was suspected and a relaparotomy was performed. A small pressure ulcer of the pancreatic head of the donor pancreas because of dislocation of a per-operative placed drain without anastomotic leakage was found. The other patient developed an entero-cutaneous fistula after a per-operative taken biopsy of the donor pancreas. This was not considered as conversion-related, because pancreas biopsies were not routinely performed during our conversion procedure.

The median pre- and post-conversion daily oral intake of sodium bicarbonate was 12.7 and 0 gram, respectively ($p< 0.0005$).The median 24-hour urinary protein and uri-

Table 2 Complications after enteric conversion

Complication	number
Cystitis	n=7 (14%)
Paralytic ileus	n=1 (2%)
Phlebitis	n=1 (2%)
Self-limiting bleeding	n=1 (2%)
Low-grade wound infection	n=2 (4%)
Relaparotomy	n=1 (2%)*

nary sodium loss were 1.4 and 0.3 gram ($p< 0.0005$), and 344 and 190 mmol ($p <0.0005$), respectively (Table 3). No change in antihypertensive drug therapy was found in 35 patients. In 10 patients, an increase was found, whereas in 5 patients, a decrease. In one patient, these data were missing. The renal clearance and endocrine pancreatic function 6 months before and after conversion were not significantly different. (Table 3)

One-year patient, pancreas graft and kidney graft survival rates after enteric conversion were 100, 98 and 100%, respectively. Three-year patient, pancreas graft and kidney graft survival rates after enteric conversion were 93, 93 and 97%, respectively. Two patients lost their pancreas graft after enteric conversion: one patient refused to continue immunosuppressive medication intake. The pancreas was rejected, while the kidney transplant remained functional. This patient is now considered a candidate for a pancreas after kidney (PAK) transplantation. Another patient developed an arterial thrombosis 25 months after enteric conversion (considered as not conversion related). In none of the 51 patients, rejection treatment was given in the period following enteric conversion.

In 96% of the patients, pre-conversion existing symptoms were resolved (in two cases recurrent urinary tract infections persisted).

Table 3 Clinical parameters before and after enteric conversion

	Before*	After*	*P*-value
Sodium Bicarbonate intake/day (gram)	12.7	0	< 0.0005
Urinary protein loss/day (gram)	1.4	0.3	< 0.0005
Urinary sodium loss/day (mmol)	344	190	< 0.0005
Pancreas function (HbA1c)(%)	5.4	5.3	ns
Renal clearance (ml/min)	56.3	57.2	ns

* median, ns = not significant

DISCUSSION

In this study, we showed the safety and the beneficial effect of enteric conversion of the pancreas after SPK with primary bladder drainage. Although in some studies duodenal leakage and abscess formation leading to surgical reintervention were found after enteric conversion (8,16-18), we did not find any leakage at the side of the anastomosis or intra-abdominal infections. Two relaparotomies were performed and only a few minor complications were seen. No rejection treatment was needed in the period following conversion. There was no graft loss due to the enteric conversion and there were no negative effects on both the pancreatic and kidney graft function.

In the early years of pancreas transplantation, bladder drainage was the main duct management technique used. It is a relative safe procedure and especially in PTA and PAK, it has the advantage to use urinary amylase as a rejection marker for the pancreas. However, bladder drainage also has its particular complications. It creates non-physiological drainage of exocrine pancreatic fluids containing large amounts of sodium bicarbonate causing metabolic complications. Long-term urological complications develop because of pre-existing diabetes-related bladder dysfunction, surgical-related anatomic changes and the aggressive nature of pancreatic digestive enzymes combined with high urinary pH levels. Reflux-pancreatitis is another major long-term complication in bladder drainage.

These long-term urological and metabolic complications may be prevented in enteric-drained transplants. Increasing experience and success led to a tendency to perform more primary enteric drained pancreas transplantations. Despite improving results, some reports show significantly lower pancreas graft survival and higher intra-abdominal infection rates in enteric-drained than that in bladder-drained transplants (2,10-13,19-24). In case of anastomotic leakage or breakdown of the enterostomy, there is a higher risk of serious early post-operative complications (12,13). Possible risk factors for anastomotic leakage or breakdown of the enterostomy may be a poor quality of the duodenum segment as the result of ischaemia and preservation injury, difficulties with vascular and enteric anastomosis because of anatomical localization, and adhesions or poor general health of the recipient. Also, late intra-abdominal infections are reported in enteric-drained transplants (23). These intra-abdominal infections may lead to severe morbidity, and even death or graft loss. Several months after transplantation, preservation or reperfusion graft injuries and oedema of the duodenal graft have resolved, patients are in better general health, and they take smaller amounts of immunosuppressive drugs (9). These facts might explain the absence of leakage or intra-abdominal infection after enteric conversion in our patient group. Therefore, our two-step approach might be valuable in case of increased risk on anastomotic leakage of the enterostomy.

During the first months after transplantation, rejection episodes are most likely to occur. In SPK, rejection episodes of the pancreatic graft usually occur simultaneously with rejection of the kidney graft and as a consequence, creatinine levels can be used as rejection marker. In case of PAK or PTA serum creatinine levels are no longer useful as pancreas rejection marker. In PAK and PTA one-year pancreas graft survival rates were significantly higher in bladder-drained than that in enteric-drained transplants (2,7,25). Therefore, in PAK or PTA a primary bladder drainage with an enteric conversion after several months might improve graft survival outcome: urine amylase can be used as a rejection marker and early enteric drainage-related problems are avoided while the pancreas graft ends up with the more physiological and preferable drainage. However, in a previous study with prednisone, cyclosporin and azathioprin as maintenance immunosupression in the PTA group, a rejection rate of 55 % was seen after enteric conversion, resulting in a very high graft loss rate (8). In the SPK group, a rejection rate of 13% was seen (8). In the present study with prednisone, cyclosporin and mycophenolate mofetil as maintenance immunosuppression no rejection episodes were found in the SPK group following enteric conversion. Therefore, we expect that with the present immunosuppression, much less graft loss because of rejection following enteric conversion will occur in both PTA and PAK. However, future studies has to confirm this.

Conclusion: Enteric drainage is the most favourable exocrine duct management because of its physiological nature and the avoidance of long-term urological complications as seen in bladder-drained transplants. In the presence of a higher risk on anastomotic complications, primary bladder drainage may be the preferred option. In the present study, we demonstrated that primary bladder drainage followed by enteric conversion is a safe and effective procedure. Therefore, a two-step approach with primary bladder drainage followed by enteric conversion may be the best approach for a selected group of SPK transplants with a higher risk on anastomtic leakage or breakdown of the enterostomy. Our observation might also be relevant in solitary pancreas transplantation, although future studies have to confirm this.

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