Does Enteric Conversion Affect Graft Survival After Pancreas Transplantation with Bladder Drainage?

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Background: Although bladder drainage is effective for monitoring urine amylase levels to detect graft rejection, enteric drainage is performed more frequently. The optimal method for monitoring pancreatic enzyme secretions remains unclear. We investigated graft survival in recipients of bladder drainage and assessed the risk of graft rejection and failure after enteric conversion.

Material/Methods: From January 1999 to October 2015, we performed 318 pancreas transplantations at our institution. We enrolled 180 recipients who underwent pancreas transplantation with bladder drainage (82 underwent enteric conversion and the rest did not).

Results: The mean interval between pancreas transplantation and enteric conversion was 20±24 months. The graft survival rate was significantly higher in the enteric conversion group for 10 years after pancreas transplantation than in the maintain bladder drainage group. After enteric conversion, 14 recipients lost graft function. The interval between enteric conversion and graft failure was 43±26 months. In the enteric conversion group, immediate postoperative thromboembolectomy (HR=12.729, p=0.000), renal failure (HR=5.710, p=0.005), pancreas graft rejection after EC (HR=19.006, p=0.000), and delayed graft function (HR=7.021, p=0.001) had a significant relationship with graft failure.

Conclusions: Enteric conversion can be safe and effective for improving short- and long-term graft survival if performed after approximately 9 months. Caution should be exercised with enteric conversion if recipients have a history of thromboembolectomy, delayed graft function, or renal failure.

MeSH Keywords: Drainage • Graft Survival • Pancreas Transplantation • Pancreas, Exocrine

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Background

Since pancreas transplantation (PT) was introduced in 1966, it has been regarded as a definitive treatment for diabetes mellitus (DM) and has been performed worldwide [1–3]. Various surgical techniques for graft implantation have been reported, and one of the most controversial issues has been the management of exocrine pancreatic secretions [1]. According to the International Pancreas Transplant Registry, bladder drainage is a commonly used method for exocrine drainage [2,3]. It has several advantages [2–4], such as safety and enabling monitoring of urine amylase level to detect graft rejection [4,5]. However, bladder drainage (BD) can be associated with reflux pancreatitis, metabolic acidosis, and urologic complications such as recurrent urinary tract infection, hematuria, and urethritis [4–6]. Because of these drawbacks, physiologic enteric drainage has been performed in 90% of cases in the United States from 2010 to 2014 [2]. However, whether enteric or bladder drainage results in better graft survival remains unclear and the optimal method for managing pancreatic exocrine secretions remains controversial.

At our institution, BD has been performed for recipients who undergo pancreas transplant alone (PTA), pancreas after kidney transplant (PAK), and simultaneous cadaveric pancreas and living donor kidney transplant (SPLK). According to the severity of complications that lead to readmission caused by recurrent urological and metabolic complications, enteric conversion (EC) may be performed. We monitor and prevent graft rejection through delayed EC after PT using bladder drainage.

We have experienced some cases of pancreas graft rejection or failure after EC within a short period. Therefore, we investigated pancreas graft rejection and survival of recipients with bladder drainage who underwent EC compared with those who did not.

Material and Methods

Study population

From January 1999 to October 2015, we performed 318 PTs at our institution. Of these cases, 138 underwent enteric drainage, while 180 underwent BD. We enrolled the 180 recipients who underwent PT with bladder drainage (BD) in the present study. Of these, 97 received PTA, 10 received simultaneous pancreas–kidney transplant (SPK) from a deceased donor, 35 received SPLK, and 38 received PAK. The recipients with bladder drainage were divided into 2 groups according to whether they underwent EC or not: the EC group (n=82) and the maintain BD group (n=98) (Figure 1).

Figure 1. Study population of pancreas transplantation according to exocrine drainage.

The study was approved by our Institutional Review Board (S2015-1965-0002). The need for informed consent was waived because this was a retrospective study. The study was conducted in accordance with the 2008 Declaration of Helsinki.

Surgical procedure

The pancreas graft was placed on the right side of the pelvis with an arterial anastomosis to the iliac artery and venous anastomosis to the iliac vein. The pancreas graft duodenum was then anastomosed to the urinary bladder using two-layer side-to-side hand-sewn sutures. We selectively performed EC in recipients who had recurrent urological and metabolic complications such as urinary tract infection, hematuria, reflux graft pancreatitis, and metabolic acidosis. During EC, the duodenocystostomy was isolated and divided. Subsequently, the cystostomy was closed in 2 layers, and side-to-side duo- denoenterostomy was created between the graft duodenum and jejunum, followed by distal side-to-side jejunojejunostomy using a hand-sewn two-layer approach. Roux-en-Y reconstruction was performed in recipients with significant intestinal adhesions or a shortened and thickened mesentery.

Data analysis

The clinical characteristics of the patients, such as the demographics, duration and history of DM, amount of insulin, and complications of DM, were analyzed. The following data were collected for each patient with regard to the date of EC: indication of EC, time interval between PT and EC, presence of graft rejection before and after EC, and incidence of graft loss. Rejection was diagnosed clinically or by biopsy. Delayed graft function was defined as total cumulative insulin requirement of 19U or greater within postoperative 7 days based on our
Previous report [7]. Graft loss was defined as removal of the graft or re-initiation of exogenous insulin therapy. We compared the difference in graft survival between the EC and control groups and analyzed the risk factors for graft failure after EC.

Statistical analysis

The categorical variables were analyzed with absolute and relative frequencies using the $\chi^2$ test. Quantitative variables were analyzed using mean and standard deviations, and differences between the means were analyzed using Student’s $t$ test.
Graft survival was calculated using the Kaplan–Meier estimator and log-rank tests, and risk factors for graft failure were analyzed using the Cox proportional hazards regression model. Statistical calculations were performed using SPSS version 21.0 statistical software (SPSS, Chicago, IL), and p<0.05 was considered statistically significant.

Results

Characteristics and pancreas graft survival of recipients with bladder drainage

Among 180 recipients who underwent PT with bladder drainage, 82 (45.6%) underwent EC. Table 1 shows the demographic and clinical characteristics of recipients with or without enteric drainage. The age of DM onset was younger and there were more female recipients in the EC group. The patients in the EC group had significantly more DM retinopathy. The others were not significantly different.

During the follow-up period, reflux pancreatitis (p=0.024), metabolic acidosis (p=0.000), hematuria (p=0.001), and urinary tract infection (p=0.003) were significantly more frequent in the EC group (Table 2). Failure of the native kidney in PTA recipients or failure of the graft kidney and pancreas in SPK, PAK, and SPLK recipients was more frequent in the EC group, but the differences were not significant (Table 2).

The mean interval between PT and EC was 20±24(range 2–124, median 11.5) months. Indications for EC were recurrent urinary tract infection (n=27, 32.9%), metabolic acidosis (n=27, 32.9%), reflux pancreatitis (n=16, 19.5%), hematuria (n=11, 13.4%), and leakage of pancreatic enzyme (n=1, 1.2%).

The pancreas graft survival rate was significantly higher in the EC group for 10 years after PT than in the maintain EC group. However, after 10 years, the graft survival rate became higher in the maintain EC group (Figure 2). To evaluate the difference of pancreas graft survival according to their transplant type, we subdivided the patients into 4 groups (SPK, PAK, PTA, and SPLK). In SPK, PAK, and SPLK groups, there were no significant differences in graft survival between the enteric conversion group and the maintain EC group (p=0.251, 0.690, and 0.750, respectively). However, we found that the pancreas graft survival in the enteric conversion group was significantly higher than in the maintain EC group (p=0.002) (Figure 3). In the PTA group, the risk of pancreas graft failure was significantly lower in the enteric conversion group (HR=0.254, 95% confidence interval 0.101-0.637, p=0.003)

We analyzed the risk factors for pancreas graft failure after bladder drainage. In univariate analysis, recurrent urinary tract infection [hazard ratio (HR)=0.762, p=0.025], renal failure (HR=2.078, p=0.022), and a history of previous pancreas graft rejection (HR=3.558, p=0.000) increased the risk of graft failure, whereas EC (HR=0.395, p=0.005) lowered the risk. However, in multivariate analysis, EC (HR=0.309, p=0.000)

| Table 2. Post-transplant complications in recipients. |
|-----------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                   | Enteric         | Maintain EC    | p-Value        | No graft failure | Graft failure  | p-Value        |
|                                   | conversion (n=82) | (n=98)         |                | (n=68)          | (n=14)         |                |
| Postoperative bleeding            | 7 (8.5%)        | 18 (18.4%)     | 0.058          | 4 (5.9%)        | 3 (21.4%)      | 0.058          |
| Thrombosis                        | 23 (28.0%)      | 36 (36.7%)     | 0.213          | 21 (30.9%)      | 2 (14.3%)      | 0.208          |
| Thromboembolectomy                | 3 (3.7%)        | 6 (6.1%)       | 0.450          | 2 (2.9%)        | 1 (7.1%)       | 0.446          |
| Leakage                           | 5 (6.1%)        | 1 (1.0%)       | 0.059          | 4 (5.9%)        | 1 (7.1%)       | 0.858          |
| Reflux pancreatitis               | 31 (37.8%)      | 22 (22.4%)     | 0.024          | 23 (33.8%)      | 8 (57.1%)      | 0.101          |
| Metabolic acidosis                | 39 (47.6%)      | 18 (18.4%)     | 0.000          | 28 (42.1%)      | 11 (78.6%)     | 0.011          |
| Hematuria                         | 25 (30.5%)      | 10 (10.2%)     | 0.001          | 19 (27.6%)      | 6 (42.9%)      | 0.270          |
| Urinary tract infection           | 59 (72.0%)      | 49 (50.0%)     | 0.003          | 50 (73.5%)      | 9 (64.3%)      | 0.483          |
| Kidney failure                    | 11 (13.4%)      | 5 (5.1%)       | 0.051          |                |               |                |
| Past history of pancreas graft rejection | 21 (25.6%)      | 16 (16.3%)     | 0.125          |                |               |                |
| Pancreas graft failure            | 14 (17.1%)      | 28 (28.6%)     | 0.069          |                |               |                |
and a history of previous pancreas graft rejection (HR=17.499, p=0.001) had a significant relationship with graft failure (Table 5).

Figure 2. Differences in graft survival after pancreas transplantation between the enteric conversion group and the maintain bladder drainage group.

Figure 3. Differences in graft survival after pancreas transplantation between the enteric conversion and the maintain bladder drainage group in PTA patients.

Discussion

Enteric drainage is obviously more beneficial physiologically for managing exocrine secretions after a pancreas graft [1–4]. However, bladder drainage remains an important alternative because of its significant advantages in monitoring urinary amylase as a rejection marker for the pancreas [4]. The rejection of pancreas grafts occurs frequently and is often irreversible when hyperglycemia occurs; hence, bladder drainage is preferred over enteric drainage, particularly with solitary PTs. However, bladder drainage leads to several urologic and metabolic complications, such as urinary tract infection, which can affect graft survival [4]. Graft survival of the pancreas according to the type of exocrine drainage employed remains a controversial issue [8–11]. Grussner and Sutherland [9] showed that graft survival after 1 year was slightly lower in the group that received EC than in the group that received bladder drainage (72% vs. 79%) but this difference was not significant. However, the 1-year graft rejection rate was significantly higher in the group that received EC than in the group that received bladder drainage (14.6% vs. 5.4%). These results demonstrate that low urine amylase can be detected with bladder drainage, and treatment can be initiated at an earlier stage. Cory et al. [10] reported that recipients who underwent enteric drainage had a lower graft survival rate than those who underwent bladder drainage (77% vs. 88% at 6 months; 69% vs. 77% at 1 year), but this difference was not significant at follow-up. However, some studies showed excellent long-term outcomes for bladder

Pancreas graft survival

| Drainage type | Enteric conversion | Maintain bladder drainage |
|---------------|--------------------|--------------------------|
| Follow-up after pancreas transplantation (months) |
| 1-year        | 100% (8)           | 82.9% (16)               |
| 3-year        | 93.1% (5)          | 72.4% (23)               |
| 5-year        | 84.4% (9)          | 63.6% (26)               |
| 7-year        | 80.4% (10)         |                          |
| 10-year       | 63.5% (13)         |                          |

In univariate analysis, re-transplantation (HR=7.948, p=0.002), immediate postoperative thromboembolectomy (HR=13.096, p=0.029), metabolic acidosis (HR=4.396, p=0.023), renal failure (HR=3.143, p=0.041), delayed graft function of pancreas (HR=9.051, p=0.000), and pancreas graft rejection after EC (HR=19.006, p=0.000) and delayed graft function (HR=7.021, p=0.000), and metabolic acidosis (HR=4.396, p=0.023), renal failure was more common in the graft failure group (Table 4). With regard to pancreas graft function, delayed graft function and graft rejection of the pancreas before and after EC were higher in the pancreas graft failure group than in the maintain EC group (Table 4).

Differences in graft survival after pancreas transplantation between the enteric conversion and the maintain bladder drainage group in PTA patients.
Table 3. Clinical characteristics of recipients with enteric conversion according to the presence of graft failure.

|                                      | No graft failure (n=68) | Graft failure (n=14) | p-Value |
|--------------------------------------|-------------------------|----------------------|---------|
| Age of recipient (years)             | 33.4±10.3               | 33.7±11.2            | 0.933   |
| Sex of Recipient (male)              | 25 (36.8%)              | 6 (42.6%)            | 0.669   |
| Type of diabetes                     |                         |                      | 0.068   |
| Type 1                               | 61 (89.7%)              | 10 (71.4%)           |         |
| Type 2                               | 7 (10.3%)               | 4 (28.6%)            |         |
| Age of DM onset (years)              | 19.3±7.7                | 17.2±8.8             | 0.370   |
| Duration of DM (years)               | 13.5±8.3                | 16.4±5.3             | 0.214   |
| Complication                         |                         |                      | 0.352   |
| Nephropathy                          | 32 (47.1%)              | 8 (57.1%)            | 0.492   |
| Retinopathy                          | 14 (20.6%)              | 2 (14.3%)            |         |
| Age of donor (years)                 | 26.1±8.3                | 30.4±9.4             | 0.089   |
| Follow-up (months)                   | 50.9±34.7               | 43.0±26.9            | 0.425   |
| Re-transplantation                   | 0                       | 1 (7.1%)             | 0.027   |
| PRA Class I                          | 7.7±25.1                | 5.7±9.2              | 0.752   |
| (MFI)                                | 116.5±467.0             | 0                    |         |
| PRA Class II                         | 3.8±9.3                 | 7.7±2.3              | 0.633   |
| (MFI)                                | 87.8±42.3               | 0                    | 0.562   |
| Cold ischemic time (min)             | 357.4±139.2             | 375.8±149.6          | 0.658   |
| Induction                            |                         |                      | 0.158   |
| Thymoglobulin                        | 58 (85.3%)              | 9 (64.3%)            |         |
| Simulet                              | 7 (10.3%)               | 4 (28.6%)            |         |
| Zenapax                              | 3 (4.4%)                | 1 (7.1%)             |         |
| Calcineurin inhibitor                |                         |                      | 0.666   |
| FKS06                                | 65 (95.6%)              | 13 (92.9%)           |         |
| Cyclosporin                          | 3 (4.4%)                | 1 (7.1%)             |         |
| Antimetabolites                      |                          |                      | 0.142   |
| MMF                                  | 51 (75.0%)              | 1 (7.1%)             |         |
| Myfortic                             | 17 (25.0%)              | 1 (7.1%)             |         |
| Corticosteroid                       |                         |                      | 0.780   |
| Time from pancreas transplantation to enteric conversion (months) | 19.1±23.5 | 26.6±28.1 | 0.299 |
| Cause of enteric conversion          |                         |                      | 0.336   |
| Urinary tract infection              | 23 (33.8%)              | 4 (28.6%)            |         |
| Metabolic acidosis                   | 22 (32.4%)              | 5 (35.7%)            |         |
| Reflux pancreatitis                  | 15 (22.1%)              | 1 (7.1%)             |         |
| Hematuria                            | 7 (10.3%)               | 4 (28.6%)            |         |
| Leakage                              | 1 (1.5%)                | 0                    |         |
drainage in addition to a lower incidence of thrombosis, early technical complications, and graft loss due to monitoring for early graft rejection and subsequent treatment [12]. At our center, the group that received enteric drainage showed significantly higher graft survival than the one that received bladder drainage (Figure 4A). Therefore, we subdivided the bladder drainage group into an EC group and a control group and compared the graft survival in all 3 groups (Figure 4B). In the EC group, there was no significant difference in graft survival between the individuals who underwent enteric drainage and those who underwent bladder drainage. However, the risk of graft failure was significantly higher in the latter group (HR=3.369, p=0.000). When we compared the effect of graft failure risk of EC according to their transplant type, EC significantly lowered pancreas graft failure risk in PTA recipients (HR=0.254, p=0.003). Based on these results, we confirm that EC significantly reduced the risk of pancreas graft failure, especially in PTA.

### Table 4. The effect of renal function and pancreas graft function on graft failure after enteric conversion.

|                                    | No graft failure (n=68) | Graft failure (n=14) | p-Value |
|------------------------------------|------------------------|----------------------|---------|
| Kidney failure                     | 7 (10.3%)              | 5 (35.7%)            | 0.014   |
| Native kidney                      | 5 (14.3%)              | 3 (50.0%)            | 0.041   |
| Graft kidney                       | 2 (6.1%)               | 2 (25.0%)            | 0.105   |
| **Graft kidney rejection**         |                        |                      |         |
| Before enteric conversion          | 7/33 (21.2%)           | 2/8 (25.0%)          | 0.816   |
| After enteric conversion           | 2/33 (6.1%)            | 0                    | 0.475   |
| **Delayed graft function of pancreas** | 0                    | 5 (35.7%)            | 0.000   |
| **Pancreas graft rejection**       |                        |                      |         |
| Before enteric conversion          | 11 (16.2%)             | 3 (21.4%)            | 0.002   |
| Interval from PT to rejection (days)| 102.3±109.2            | 470.5±586.2          | 0.075   |
| After enteric conversion           | 1 (1.5%)               | 7 (50%)              | 0.000   |
| Interval from enteric conversion to rejection (days) | 423.5±586.2 | 764.0±499.5 | 0.415 |

* Delayed graft function of pancreas was defined as a total cumulative insulin requirement of 19 UI or greater within postoperative 7 days.

### Table 5. Risk factor of pancreas graft failure after enteric conversion.

|                                    | Univariate | Multivariate |
|------------------------------------|------------|--------------|
| Postoperative bleeding             | 3.296 (0.913–11.904) | 0.069 |
| Postoperative thromboembolectomy   | 13.096 (1.300–23.190) | 0.029  | 10.924 (1.788–24.862) | 0.015  |
| Reflux pancreatitis                | 2.524 (0.873–7.294) | 0.087 |
| Metabolic acidosis                 | 4.396 (1.225–15.785) | 0.023  | 3.109 (0.816–11.846) | 0.096  |
| Re-transplantation                 | 7.948 (1.497–12.709) | 0.002  |
| Delayed graft function             | 9.051 (2.947–17.797) | 0.000  | 7.021 (2.012–23.195) | 0.001  |
| Pancreas graft rejection before enteric conversion | 1.008 (0.202–5.021) | 0.092  |
| Pancreas graft rejection after enteric conversion | 12.729 (4.260–28.031) | 0.000  | 19.006 (5.718–23.168) | 0.000  |
| Renal failure                      | 3.143 (1.050–9.410) | 0.041  | 5.710 (1.700–19.181) | 0.005  |
The reported conversion rate from bladder drainage to enteric drainage ranges from 10% to 40% [4-6]. At our center, 45.6% of recipients received EC approximately 20 months after PT and 15.9% (n=13) experienced graft rejection before EC within 253.7±33.94 (13–1125, median 101) days. After EC, there were no surgical complications such as leakage, bleeding, and re-exploration, but postoperative ileus developed in 9 recipients, recovering with conservative treatment. Many studies have reported that EC following PT does not lead to severe complications [3,5,6,11]. Our data also show that graft rejection treated adequately before EC did not increase the risk of graft failure in univariate and multivariate analyses (Table 5). A history of immediate postoperative thromboembolectomy, delayed graft function, renal failure, and pancreas graft rejection after EC were risk factors for pancreas graft failure after EC (Table 5).

Some centers perform bladder drainage as a primary procedure, particularly following solitary PT, with EC performed after several months [4,6,11]. This two-step approach is considered to improve graft outcomes because graft rejection is monitored using urine amylase in the early stages and enteric drainage-related problems can be avoided [6,11]. Long-term graft survival using this two-step approach is comparable to that in primary enteric drainage recipients. However, the approach can lead to unnecessary surgery and increases the cost and surgical complications in some recipients [11]. At our institution, the annual number of PTs (≥30 cases since 2012) has been steadily increasing, and approximately half are cases of PTA, with bladder drainage used to monitor the urine amylase level. Therefore, we tried to improve graft survival by monitoring urine amylase in early periods and perform the enteric conversion after about 9–12 months after PT if the recipient experienced the complications recurrently. This procedure has been maintained continuously at our center. In this study, our results show the benefit of enteric conversion after bladder drainage.

Our study has some limitations. It was a retrospective and single-center study with relatively few cases. However, our institute prefers bladder drainage after solitary PTs such as PTA, PAK, and SPLK. Therefore, we aimed to analyze which patients are best suited for EC.

Conclusions

Our data show that EC approximately 9 months after PT with bladder drainage is a safe and effective method for improving short- and long-term graft survival, especially in PTA. However, the use of EC is accompanied by loss of the monitoring marker for graft rejection. Therefore, before deciding on EC, caution should be exercised for recipients with a history of immediate postoperative thromboembolectomy, delayed graft function, and renal failure. After EC, close monitoring for graft function is necessary for recipients with suspected graft rejection.
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