Is the enteral replacement of externally drained pancreatic juice valuable after pancreatoduodenectomy?

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Abstract

**Purposes** External drainage of pancreatic juice using a pancreatic duct stent following pancreatoduodenectomy is widely performed. We hypothesized that the replacement of externally drained pancreatic juice would help to prevent postoperative complications, including pancreatic fistulas.

**Methods** Sixty-four patients who underwent pancreatoduodenectomy between 2006 and 2008 were randomly assigned to either a pancreatic juice non-replacement (NR) or replacement (R) group. Eighteen patients were excluded from the analysis because they had unresectable tumors (n = 4), low pancreatic juice output (<100 ml) (n = 11) or for other reasons (n = 3). A total of 46 patients (NR = 24, R = 22) were included in the final analysis. The volume and amylase levels of externally drained pancreatic juice were analyzed on postoperative days 7 and 14. The incidence of postoperative complications, including pancreatic fistulas, was also assessed.

**Results** The total amylase secretion from the pancreatic tube on postoperative day 7 was significantly higher in the NR group compared with the R group (P = 0.044). The incidence of pancreatic fistulas (>Grade B) was also significantly higher in the NR group (33.3 vs. 9.1%, P = 0.046).

**Conclusions** In cases for whom external pancreatic juice drainage from a stent is applied following pancreaticojejunostomy, enteral replacement of externally drained pancreatic juice may reduce the incidence of postoperative pancreatic fistula formation.

Keywords Pancreatic juice · Pancreatic duct stent · Feedback regulation · Amylase · Pancreatic fistula

Introduction

Pancreatic leakage is a major cause of morbidity and mortality after pancreatoduodenectomy. A high output of pancreatic juice from a soft pancreas is a risk factor for pancreatic anastomotic leakage [1]. A stenting technique for the remnant of the main pancreatic duct has been widely used to facilitate the drainage of pancreatic juice and reduce the incidence of pancreatic fistulas [2], but whether this technique is superior to a non-stenting approach is still controversial [3–7]. Nonetheless, a Japanese survey of 3,109 cases that investigated pancreatic-gastrointestinal anastomotic methods revealed that more than 80% of patients underwent external pancreatic juice drainage [8]. It is unclear whether externally drained pancreatic juice should be discarded or replaced in the gastrointestinal system.

Cholecystokinin (CCK), which is released due to a decreased proteolytic activity in the proximal intestinal lumen, stimulates the excretion of pancreatic juice [9]. After pancreatoduodenectomy, in which the duodenum is resected either completely or nearly completely, along with the head of the pancreas, duodenopancreatic reflexes transmitted by sympathetic nerves are absent. The pancreas is also reduced to approximately half of its original volume after pancreatoduodenectomy. This creates abnormal gastrointestinal physiology. However, there have been only a few reports examining the alterations in pancreatic
exocrine function after pancreateoduodenectomy [10]. In a previous study, our group described a feedback regulation mechanism controlling the basal pancreatic juice secretion in patients who underwent pancreateoduodenectomy [11]. Enteral replacement of externally drained pancreatic juice following pancreateoduodenectomy resulted in a significant (30 %) decrease in water, protein, bicarbonate and enzyme output compared with the levels in patients who did not undergo replacement [11]. Therefore, we hypothesized that enteral re-infusion of externally drained pancreatic juice after pancreateoduodenectomy would attenuate the basal pancreatic secretion and reduce the risk of pancreatic fistulas. To study this hypothesis, we randomly assigned patients who underwent pancreateoduodenectomy with child reconstruction into pancreatic juice replacement (R) and non-replacement (NR) groups and compared the clinical outcomes between the two groups.

**Patients and methods**

**Patients**

From April 2006 to August 2008, 64 pancreateoduodenectomies were performed in the First Department of Surgery, Nagoya University Hospital. Preoperative biliary drainage was performed when hyperbilirubinemia or biliary dilatation and hepatic dysfunction were detected. Surgery was performed when the serum total bilirubin levels decreased below 2 mg/dl. All clinical and biochemical data analyzed in this study were collected prospectively.

**Surgical techniques**

All patients underwent either a pylorus-preserving, subtotal stomach-preserving or conventional pancreateoduodenectomy with child reconstruction. In pylorus-preserving pancreateoduodenectomy, the proximal duodenum was preserved 2–4 cm distal to the pylorus. In subtotal stomach-preserving pancreateoduodenectomy, the stomach was dissected by a linear stapler approximately 3 cm proximal to the pylorus. In conventional pancreateoduodenectomy, a distal gastrectomy (approximately 50 % of the stomach) was performed. The pancreatic gland texture was assessed by the surgeon intraoperatively and then was classified as either soft or firm. The pancreatic anastomosis was performed by duct-to-mucosa pancreaticojejunostomy using 5-0 absorbable monofilament sutures and end-to-side pancreaticojejunostomy using 4-0 nonabsorbable monofilament sutures in all patients. The number of stitches varied depending on the size of the pancreas body and main pancreatic duct. No pancreaticogastrostomies were performed. In all cases, a polyethylene knotted pancreatic duct drainage tube (Sumitomo Bakelite Co., Tokyo, Japan) (Fig. 1) was inserted into the main pancreatic duct of the remaining pancreas, and the tube was exteriorized through the end of the blind loop of the jejunum. Different sizes of pancreatic duct drainage tubes (4–7.5 Fr) were used depending on the size of the main pancreatic duct. Because of the knot in the tube, most of the pancreatic juice secreted from the pancreas remnant was drained and collected in a bottle. An 8-Fr polyethylene jejunal tube was separately inserted as a route for enteral nutrition and replacement of pancreatic juice in the replacement group (R group). The tip of this enteral tube was placed distal to the duo- nojejunal or jejunogastric anastomosis. In the nonreplacement group (NR group), tubes were placed as in the R group, but pancreatic juice was discarded without re-infusion. A 10-mm Penrose drain (a silicone multitubular flat drain) was placed at the dorsal and ventral sides of the pancreaticojejunostomy.

Proton pump inhibitors and H2-blocker were not used routinely after surgery, unless we suspected the presence of a gastric ulcer. Moreover, no patient received octreotide administration, even in the cases with severe pancreatic fistulas. The same nutrition support protocol was used for both the R and NR groups.

Of the 64 enrolled patients, four patients were excluded from the study due to severe local invasion of the tumor or liver metastases incidentally found at laparotomy (Fig. 2). Therefore, 60 patients underwent the pancreateoduodenectomy. Two patients (one in the NR group and one in the R
Patients enrolled (n=64)

Inoperable due to severe local invasion or liver metastasis

Non-replacement of pancreatic juice (n=30)

Replacement of pancreatic juice (n=30)

Excluded due to dislocation of pancreatic tube

Excluded due to re-operation

Non-replacement of pancreatic juice (n=29)

Replacement of pancreatic juice (n=28)

Less than 100ml daily discharge from pancreatic tube

Non-replacement of pancreatic juice (n=24)

Replacement of pancreatic juice (n=22)

Fig. 2 Details about the patients included in this study

Blood was collected within 1 week prior to surgery and on postoperative days 7 and 14. These samples were analyzed for the serum amylase, lipase, trypsin, total protein, albumin, choline esterase, sodium (Na), calcium (Ca) and zinc (Zn) levels. The daily volume of pancreatic juice collected from the pancreatic duct stenting tube was measured and recorded. On postoperative days 7 and 14, the amylase levels in the externally drained pancreatic juice were also measured, and the daily output of amylase from the pancreas remnant was calculated by multiplying the concentration of amylase by the volume of drained pancreatic juice.

Postoperative pancreatic fistulas and delayed gastric emptying were classified according to the criteria of the International Study Group of Pancreatic Surgery (ISGSP) [12, 13]. The “Classification of surgical complication after pancreatic surgery” by DeOliveira et al. [14] was used to assess complications after pancreatoduodenectomy.

Statistics

The sample size was calculated based on the premise of decreasing the rate of pancreatic fistula from 40 % in the NR group to 10 % in the R group, with the α value set at 0.05 and the β value set at 0.2 (yielding a power of 80 %). These calculations indicated that we needed to include approximately 25 patients in each group. The results were expressed as the means ± standard deviations or standard errors. Continuous data between two groups were compared using Student’s t test. Categorical data were compared using the χ² test or Fisher’s exact test, where appropriate. A result was considered to be statistically significant when P < 0.05. All statistical analyses were performed using the SPSS software program (Version 13.0, Chicago, IL, USA).

Results

Patient characteristics

The clinical characteristics of the study population stratified by whether they received pancreatic juice replacement are described in Table 1. All of the preoperative and intraoperative factors described in Table 1 did not differ significantly between the two groups. The factors that have been reported to be associated with the occurrence of pancreatic fistulas, including the body mass index [15, 16], diabetes mellitus [17], size of the main pancreatic duct [18], texture of the pancreas [15] and intraoperative bleeding [19], did not differ significantly between the two groups.
Blood tests

The serum pancreatic enzyme levels of amylase, lipase and trypsin were not significantly different between the NR and the R groups (Fig. 3a). Compared with preoperative values, the mean pancreatic enzyme levels on postoperative day 7 were significantly lower in both the NR and R groups, and these levels were sustained through postoperative day 14. The serum total protein, albumin, and choline esterase levels also showed a similar trend (Fig. 3b).

Pancreatic juice is known to contain high amounts of sodium (Na), calcium (Ca) and zinc (Zn) [20, 21]. We hypothesized that the disposal of pancreatic juice drained from the main pancreatic duct tube would reduce the serum Na, Ca and Zn levels in the NR group compared with the R group. However, unexpectedly, the serum Na, Ca, and Zn levels were not significantly different between the two groups (Fig. 3c).

Daily discharge of pancreatic juice from the pancreatic drainage tube

The daily discharge of pancreatic juice tended to be lower in the R group in the first week compared with the NR group, probably due to the negative feedback regulation mechanism described previously [11]. However, in the second week, there was no statistically significant difference between the two groups (Fig. 4). Interestingly, the total pancreatic amylase output from the pancreatic duct stent tube, which was calculated as the product of the daily amount of pancreatic juice discharge (ml) and the amylase content in pancreatic juice (IU/l), was significantly lower in the R group than in the NR group on postoperative day 7 (Fig. 5).

Postoperative complications

There were no surgery-related deaths in either group. The overall complication rate observed during the postoperative course was 75.0 % (18/24) in the NR group and 59.1 % (13/22) in the R group, respectively. There were no differences in the overall incidence of pancreatic fistulas between the two groups (NR vs. R; 58.3 vs. 36.4 %). However, the incidence of severe pancreatic fistulas (Grade B and C) was significantly higher in the NR group (33.3 %) than the R group (9.1 %) (Table 2). The rates of other complications, including delayed gastric emptying, were not significantly different between the two groups. The postoperative hospital stay was significantly longer in the NR group than in the R group.

Table 1 Characteristics of the study population stratified by pancreatic juice replacement

<table>
<thead>
<tr>
<th></th>
<th>Non-replacement (n = 24)</th>
<th>Replacement (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>63.3 (43–85)</td>
<td>63.1 (44–79)</td>
<td>0.930</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>15/9</td>
<td>13/9</td>
<td>0.813</td>
</tr>
<tr>
<td>Body mass index, kg/m² [SD]</td>
<td>21.3 [3.2]</td>
<td>22.3 [3.2]</td>
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</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>5 (20.8)</td>
<td>1 (4.5)</td>
<td>0.190</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (20.8)</td>
<td>6 (27.3)</td>
<td>0.734</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>0</td>
<td>2 (9.1)</td>
<td>0.223</td>
</tr>
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<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td>0.257</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>11 (45.8)</td>
<td>8 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3 (12.5)</td>
<td>9 (40.9)</td>
<td></td>
</tr>
<tr>
<td>IPMN</td>
<td>3 (12.5)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Ampulla of Vater cancer</td>
<td>4 (16.7)</td>
<td>3 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3 (12.5)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Size of main pancreatic duct, mm [SD]</td>
<td>2.7 [1.6]</td>
<td>3.5 [2.1]</td>
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<td>Type of surgery, n (%)</td>
<td></td>
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<tr>
<td>PPPD</td>
<td>17 (70.8)</td>
<td>12 (54.5)</td>
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<tr>
<td>SSPPD</td>
<td>4 (16.7)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>3 (12.5)</td>
<td>9 (40.9)</td>
<td></td>
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<td>Soft pancreas, n (%)</td>
<td>14 (70.8)</td>
<td>15 (68.2)</td>
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<td>Length of operation, min [SD]</td>
<td>490 [105]</td>
<td>492 [96]</td>
<td>0.962</td>
</tr>
<tr>
<td>Intraoperative bleeding, ml [SD]</td>
<td>1,446 [1,273]</td>
<td>1,256 [467]</td>
<td>0.513</td>
</tr>
<tr>
<td>Allogeneic blood transfusion, n (%)</td>
<td>5 (20.8)</td>
<td>4 (18.2)</td>
<td>1.000</td>
</tr>
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</table>
**Discussion**

With improvements in perioperative management, pancreatoduodenectomy is now performed with a low mortality rate in high-volume centers [14, 22]. However, the postoperative morbidity rates are still high, ranging from 30 to 40%. Pancreatic fistula is the major complication after pancreatoduodenectomy, and extensive research has been performed to identify ways to avoid this complication. The use of octreotide [23], application of fibrin glue [24], and modification of reconstruction techniques [25] have shown some benefit in reducing the incidence of pancreatic fistulas. However, their definite value is still controversial. Patients with a soft pancreas, normal main pancreatic duct diameter and relatively high pancreatic juice output have been considered to be at high risk for pancreatic...
anastomotic leakage [1, 18]. In these patients, external drainage of pancreatic juice through a stent in the main pancreatic duct is considered to be a useful procedure to avoid severe pancreatic fistulas [2, 26]. However, it is unclear whether externally drained pancreatic juice, which ranges from 100 to 300 ml per day in a normal pancreas [11, 27], should be discarded or re-infused into the intestinal lumen, because pancreatic juice contains major digestive enzymes and high concentration of electrolytes. Moreover, our previous study suggested that external drainage of pancreatic juice may enhance pancreatic juice secretion due to a lack of negative feedback regulation [11]. Increased pancreatic juice secretion may increase the occurrence of postoperative pancreatic fistulas. Therefore, this study was designed to evaluate the impact of pancreatic juice re-infusion on the physiological dynamics of pancreatic juice secretion and the incidence of pancreatic fistula formation after pancreatoduodenectomy.

Studies examining the exocrine pancreatic function in the early period after pancreatoduodenectomy are very rare. Ohshio et al. [10] analyzed the volume and amylase activity of pancreatic juice in 39 patients who underwent pancreatoduodenectomy. According to their study, exocrine pancreatic function was inhibited in the first 8 days (amylase activity $23,700 \pm 4,300$ IU/day) and recovered on days nine to 15 ($48,000 \pm 8,400$ IU/day) in patients with a normal pancreatic function. Our data also showed a
similar trend. On day 7, the total amylase secretion was approximately 24,000 IU/day and recovered to 58,000 IU/ day on day 8 in the NR group (Fig. 5). Interestingly, the level of total amylase secretion on day 7 in the R group was almost half of that in the NR group. These data support our previous report, which revealed a negative feedback mechanism that regulates pancreatic juice secretion after pancreatoduodenectomy [11].

The daily pancreatic juice output from the pancreatic duct tube increases gradually between days 1 and 7 after panreatoduodenectomy [28]. Somatostatin and its analogs are known to reduce exocrine pancreatic secretion and they have been used following pancreatic surgery to reduce the risk of pancreatic fistulas [29–32]. With the same intention, we re-infused the externally drained pancreatic juice through an enteral tube to reduce exocrine pancreatic secretions. As was expected, the daily pancreatic juice secretion tended to be lower in the R group compared with the NR group during the first postoperative week, although the difference was not significant. Moreover, the daily amylase secretion on postoperative day 7 was significantly lower in the R group than the NR group. However, the difference was not evident in the next week. The overall incidence of postoperative pancreatic fistulas was not significantly different between the two groups. However, the incidence of grade B and C postoperative pancreatic fistulas was significantly lower in the R group. Our previous study demonstrated that enteral replacement of externally drained pancreatic juice resulted in a significant (30 %) decrease in the pancreatic juice output compared with the levels in patients who did not undergo replacement. Therefore, we speculate that the mechanism responsible for the lower rate of pancreatic fistula formation in the R group may be partly explained by a suppression of pancreatic juice secretion due to negative feedback regulation by pancreatic juice replacement. We also speculate that the internal stent may be effective in reducing the incidence of pancreatic fistula by decreasing pancreatic juice secretion. To the best of our knowledge, this is the first study that has analyzed the value of pancreatic juice replacement after pancreatoduodenectomy with physiological data on exocrine pancreatic function.

It should be noted that this study is not adequately powered due to the small number of studied patients. Moreover, the results of this study revealed that the concentration of amylase in the pancreatic juice and the amount of pancreatic juice secreted during the postoperative course are highly variable in each patient. Because of these limitations, it is difficult to make any definitive conclusions. A larger well-controlled study that equalizes the risk factors for pancreatic fistula formation will be necessary to precisely elucidate the impact of pancreatic juice replacement on the incidence of postoperative complications following pancreatoduodenectomy, including pancreatic fistula formation.

In summary, this study was the first to examine the impact of externally drained pancreatic juice replacement following pancreatoduodenectomy. Enteral replacement of externally drained pancreatic juice may be useful to reduce the incidence of postoperative pancreatic fistulas by attenuating the secretion of pancreatic juice. However, this physiological alteration may have little impact on the postoperative course of pancreatoduodenectomy.

Conflicts of interest Yukihiro Yokoyama and the co-authors have no conflicts of interest to declare.

References
