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Pancreatic Leakage Test in Pancreaticoduodenectomy: Relation to Degree of Pancreatic Fibrosis, Pancreatic Amylase Level and Pancreatic Fistula

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Abstract

Background: Pancreatic fistula is major source of postoperative morbidity or mortality. Soft pancreas has been considered to be one of the most important risk factors for pancreatic fistula. The purpose of the study is to clarify the relationship among extravasation of pancreatic secretions from the pancreatic stump, the pancreatic texture and clinical pancreatic fistula after pancreaticoduodenectomy.

Methods: For nineteen patients who were treated between July 2007 and August 2008, we performed intraoperative pancreatic leakage test to confirm the extravasation of pancreatic secretions from the pancreatic stump. Degree of fibrosis at the cut surface of the pancreas was reviewed blindly.

Results: Serum pancreatic amylase increased on first postoperative day (POD) and returned to preoperative level on 3POD. These change were inversely correlated with fibrosis (P < 0.001), namely the amylase level in patients with normal to mild fibrotic pancreas showed marked increase on 1POD, but not in those with moderate to severe fibrotic pancreas. Positive pancreatic leakage test was recognized in five patients (26.3%), four of 9 patients with soft pancreas (44.4%) and one of 10 with hard pancreas (10.0%). In soft pancreas, all four cases showing positive leakage test developed pancreatic fistula after pancreaticoduodenectomy, while one positive case in hard pancreas did not develop pancreatic fistula.

Conclusion: The extravasation of pancreatic secretions from the pancreatic stump occurred frequently in soft pancreas, which might result in postoperative pancreatic fistula. Therefore we should take care in treating branched duct as well as main pancreatic duct at the pancreatic stump of soft pancreas.

Key words: Pancreaticoduodenectomy · Pancreatic fistula · Soft pancreas · Leakage test · Branched pancreatic duct

Introduction

Pancreateicoduodenectomy (PD) is a major and complex surgical procedure. Recent advances in surgical technique have reduced the mortality rate after PD to below 5% in high-volume centers but operative morbidity has remained high1)~4). Many reports have said that one of the most important reasons for the morbidity after PD is pancreatic fistula5)~8). The incidence of pancreatic fistula is reported from 0% to 40% in the literature9)~10). Among many factors affecting pancreatic fistula reported,10)~20) soft pancreatic texture seems to be one of the most important risk factor for pancreatic fistula11)~20). However, the detailed mechanisms of pancreatic fistula in...
soft pancreas have not been well mentioned. In an attempt to clarify the mechanism in pancreatic fistula, we performed intraoperative pancreatic leakage test since August 2007. In the present study, we report the results of pancreatic leakage test in 19 cases of PD.

**Patients and Methods**

**Patients**

Between January 2003 and August 2008, 61 consecutive patients underwent pancreatico-duodenectomy for variable diseases at Kyushu Cancer Center Hospital, Fukuoka, Japan. Since July 2007, we performed intraoperative pancreatic leakage test (n = 19). For these patients, serum pancreatic amylase levels were measured on preoperative, 1, 3 and 7 postoperative day (POD) respectively. Among the remaining 42 patients without performing the pancreatic leakage test, 25 patients fully equipped with perioperative serum pancreatic amylase level were selected as control to know whether the pancreatic leakage test had influence on the pancreas or not. Perioperative clinical data for the patients with the leakage test and control are present in Table 1.

**Surgical Procedures**

The parenchymal tissue of the pancreas is carefully divided by using a back of a scalpel until the main pancreatic duct becomes visible. The main pancreatic duct is then isolated at a sufficient distance. To perform pancreatic leakage test, an adequate size of Atom Multipurpose Tube (Atom Medical Co., Tokyo, Japan) is inserted into the main pancreatic duct and ligated circumferentially. Two to 3 mL of diluted Indigocarmine solution was inserted into the pancreatic duct through the tube slowly. With this procedure we could recognize small pancreatic leakage sites on the cut pancreatic surface and could repair these sites, mainly by Z-suturing using 4-0 or 5-0 PDS™II (Johnson & Johnson Medical k. k., Tokyo, Japan) sutures. After this procedure, the tube was pulled out.

End-to-side pancreaticojejunostomy was performed with duct-to-mucosa anastomosis technique. For duct-to-mucosa anastomosis, interrupted suture was performed in three to five stitches with 5-0 absorbable suture at the posterior wall. After tying posterior suture, an adequate size of pancreatic tube with a knot (SUMITOMO BAKELITE Co., Ltd., Tokyo, Japan) was inserted into the pancreatic duct then ligated by the one of the absorbable suture using posterior suture. Outerrupted suture was performed in three to five stitches with 5-0 absorbable suture for anterior suture, and was followed by 3-0 Prolene suture for approximating the pancreatic parenchyma to the jejunal seromuscular layer. The pancreatic tube was used as

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical Data</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Leakage test (n=19)</td>
</tr>
<tr>
<td>Gender (M : F)</td>
<td>10 : 9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>5</td>
</tr>
<tr>
<td>Ampullary cancer</td>
<td>2</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>3</td>
</tr>
<tr>
<td>Duodenal cancer</td>
<td>1</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3</td>
</tr>
<tr>
<td>Cystic neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatic texture</td>
<td></td>
</tr>
<tr>
<td>Soft (normal : mild)</td>
<td>9 (5 : 4)</td>
</tr>
<tr>
<td>Hard (moderate : severe)</td>
<td>10 (6 : 4)</td>
</tr>
</tbody>
</table>

\*P < 0.05 versus No leak test
whether internal or external stent. Reconstruction was achieved using 1 jejunal loop with an end-to-side pancreaticojejunostomy, an end-to-side hepaticojejunostomy, and a gastrojejunostomy, mainly by the Child procedure. Two closed suction drains were placed in the vicinity of the biliary and pancreatic anastomosis.

**Perioperative management and assessments**

All patients received antibiotics (cefazolin sodium) for 72 hours, a protease inhibitor (nafamostat mesilate) for 72 hours, and a H2 blocker (famotidine) during the entire postoperative hospital course. No prophylactic somatostatin or Octreotide was used. All patients were managed in the intensive care unit for at least 24 hours. Subsequent need for stay in the intensive care unit was determined according to the patient’s condition. Since routine measurement of amylase level from the peripancreatic drains were from the 2007, pancreatic fistula for patients with leak test was evaluated by the International Study Group on Pancreatic Fistula (ISGPF) definition²¹.

**Histological Analysis**

The stump of the resected pancreas was histologically evaluated by a pathologist (K. O.) who did know neither postoperative course nor clinical data, and classified them into four categories according to fibrosis as follows: normal, mild, moderate and severe. We considered normal and mild as to soft and remainings to hard pancreas.

**Statistical Analysis**

Data were presented as mean ± standard deviation (SD) or mean ± standard error (SE). Qualitative variables were compared with a chi-square test or Fisher’s test as appropriate. Quantitative variables were compared with Student’s t-test. For the change of pancreatic amylase levels, repeated measures ANOVA was used. A P value of less than 0.05 was considered statistically significant.

**Results**

Clinical data are summarized in Table 1. Age in patients with leakage test is significantly older than those without leakage test.

**Grades of fibrosis in pancreatic stump**

Normal, mild, moderate and severe were 14, 11, 11 and 8 respectively, namely twenty-five were soft and remaining 19 were hard pancreas. Soft pancreas was recognized more in control group, but a difference was not significant (Table 1).

**Change of serum pancreatic amylase level**

Relationship between pancreatic fibrosis and perioperative serum pancreatic amylase level in all cases were shown in Fig. 1. The level on 1POD is inversely correlated with degree of fibrosis at the pancreatic stump (p < 0.001). The amylase on 1POD increased markedly in soft pancreas but not in hard pancreas. Affection of the leakage test on the pancreatic amylase level were shown in Fig. 2 In both groups, the pancreatic amylase level increased significantly on 1POD and returned to the preoperative level on 3POD. The level on 1POD in leakage test group is higher than that in no leakage test group, but difference is not significant. When these changes were analyzed according to degree of fibrosis at the stump of pancreas, the level on 1POD in soft pancreas is affected sensitively by the leakage test compared to those in hard pancreas (Fig. 3).

**Results of pancreatic leak test, and pancreatic fistula**

Among 19 patients with leakage test, leakage from the cutting surface of pancreas was recognized in five patients, three in normal, one each in mild and moderate fibrosis, namely 4 of 9 soft pancreas and one of 10 hard pancreas showed stump leakage. Clinically, pancreatic fistula was recognized in 6 patients, all were Grade A fistula, and all were with soft pancreas including the all
Table 2  Relationships among fibrosis at pancreatic stump, stump leakage, and pancreatic fistula

<table>
<thead>
<tr>
<th>Degree of fibrosis at stump of the pancreas</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft pancreas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic leakage test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3/5 (60%)</td>
<td>1/4 (25%)</td>
<td>4/9 (44%)</td>
<td>1/6 (17%)</td>
<td>5/19 (26%)</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>4/5 (80%)</td>
<td>2/4 (50%)</td>
<td>6/9 (67%)*</td>
<td>0/6 (0%)</td>
<td>6/19 (32%)</td>
</tr>
</tbody>
</table>

*p < 0.005 soft pancreas vs hard pancreas
four patients with positive leakage test. The incidence of pancreatic fistula in soft pancreas was significantly high compared to that in hard pancreas (p < 0.005). (Table 2). Sensitivity and specificity for the pancreatic fistula of the pancreatic leakage test was 66.7% and 92.3% in all cases, and 66.7% and 100% in cases with soft pancreas, respectively.

Discussion

Pancreatic anastomosis leakage remains a major cause of postoperative morbidity after pancreaticoduodenectomy. As to anastomotic leakage, many factors such as soft texture, small duct, pancreatic juice output, gender, operation factor have been reported. Among these factors, soft texture has been considered to be the most important factor, because small duct, high pancreatic output is usually found in soft texture. For anastomotic leakage, two types have been considered as follows: 1) pancreatic anastomotic leaks, and 2) extravasation of pancreatic secretions from the pancreatic stump. In addition, there were reports that even the needle hole and the seam between two anastomosed structures can be the potential site giving rise to the development of a leak. However, extravasations of pancreatic secretion from the pancreatic stump has not been clarified yet.

There have been reports mentioned on relation between exocrine activity, pancreatic texture, and pancreatic fistula. Uchida et al. reported that histological grade of fibrosis at the pancreatic stump was inversely correlated with exocrine activity. Sato et al. examined the relation between preoperative pancreatic function and leakage of pancreaticojejunoanastomosis and concluded that pancreas well preserved pancreatic function, namely soft pancreas, was risk factor for the leakage. In addition, Hamanaka et al. mentioned that soft pancreas produced more pancreatic juice and had a higher leak rate after pancreaticoduodenectomy. In this study, we examined the serum pancreatic amylase level to evaluate pancreatic injury caused by resection or the leakage test, because total amylase concentration consists of both pancreatic and salivary amylase. Our results that the strong invert relation between the fibrosis at the pancreatic stump and the amylase level are in line with above reports. In all cases, the pancreatic amylase level increased at their max on 1POD and returned to preoperative levels on 3POD, these changes were remarkable and were accelerated by the leak test in soft pancreas. These findings supported that soft pancreas had high capacity of producing pancreatic juice against stimulants.

Although no statistically difference was present because of small number of cases, cases showing secretion from the pancreatic stump confirmed by the pancreatic leakage test were more in patient with soft pancreas compared to those with hard pancreas, suggested that many branched pancreatic duct communicating with the main pancreatic duct were present at the stump in soft pancreas. In soft pancreas, even if leakage point was closed, or cases showing negative result in the leakage test, postoperative pancreatic fistula was occurred frequently. These were probably due to extravasation from many branched ducts without communicating the main pancreatic duct, which were not confirmed by leakage test, or leakage from the needle hole or seam between two anastomosed structures in soft pancreas with high pancreatic juice output. On the other hands, pancreatic fistula was occurred in only one case in hard pancreas, which were suggested that most branched ducts were replaced by fibrosis and even if the ducts were presented, output was less and it would be sealed by approximating anastomosis.

Murakami et al. examined both serum and drain pancreatic amylase levels and reported that both levels in soft pancreas increased significantly higher than those in hard pancreas, which also support that extravasation from the stump of the soft pancreas after pancreaticoduodenectomy.
were paralleled with increase of serum amylase level. Okabayashi et al.\textsuperscript{15} analyzed the risk factors for pancreatic fistula and concluded that soft texture and increased serum amylase level on POD1 were the predictable factors for fistula. From our findings and above reports, pancreas with higher amylase level on POD1 would reflect productivity of pancreatic juice and tend to cause extravasation from the pancreatic stump.

There are controversies as to pancreaticojejunostomy including a duct to mucosa anastomosis and an invagination anastomosis.\textsuperscript{26-27} Duct to mucosa pancreaticojejunostomy or Kakita methods were essentially that approximate the pancreatic stump and jejunal wall that left no dead space between the jejuna wall and the pancreatic stump to seal the extravasation of pancreatic secretions from the pancreatic stump.\textsuperscript{28} These methods are possible and reasonable for hard pancreas, because hard pancreas secreted less pancreatic juice and is hard enough to approximate the pancreatic stump and jejuna wall. Whereas some cases in soft pancreas, it seems to be difficult because it is too fragile to tie enough without dead space between the jejuna wall and the pancreatic stump which have high exocrine output, although there were reports that duct to mucosa pancreaticojejunostomy could be used regardless of pancreatic texture.\textsuperscript{29-30}

Marcus et al.\textsuperscript{17} reported that although end to side pancreaticojejunostomy was acceptable for low-risk patients, it did not appear safe for high-risk patients and jejunal invagination of the pancreatic remnant appeared to be a safe technique for high-risk patients. Yang et al.\textsuperscript{31} reported that anastomatic techniques should be selected based on the status of the remnant pancreas intraoperatively as follows: duct-to-mucosa anastomosis for patients with dilated duct, and invagination anastomosis for soft pancreas. Ohigashi et al.\textsuperscript{32} reported that invagination technique to drain the pancreatic juice secreted from the cut surface by using mattress sutures to prevent laceration reduced the postoperative leakage. Peng et al.\textsuperscript{23} introduce the binding pancreaticojejunostomy without pancreatic leakage.

In this series, we did not use invagination methods, but our results of leakage test and above findings, to protect the secretion from the cut surface of the soft pancreas, total drainage methods like invagination methods might be better than approximating methods like duct-to-mucosa anastomosis.

In conclusion, operative pancreatic leakage test itself did not prevent postoperative pancreatic fistula, but, by this test, we got to know that the leakage from branched pancreatic ducts at the cut surface of the soft pancreas was comparatively high, which may result in postoperative pancreatic fistula. In soft pancreas, it is important that we pay attention to branched duct in the same way as the main pancreatic duct enough. Further studies in pancreaticojejunostomy for soft pancreas are needed.

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膵頭十二指腸切除術における膵管リークテストの有用性；膵繊維化の程度と血清アミラーゼ値、膵液漏との関係

足立英輔1, 播本憲史1, 山下洋市2, 坂口善久1, 森田 勝3, 川中博文3, 池田哲夫3, 前原喜彦3

はじめに
膵液漏は膵切除術合併症で特に問題となる合併症である。Soft pancreas は膵液漏の危険因子と言われている。今回膵切離断端からの膵液の漏れと、膵の繊維化の程度、膵液漏の発生との関連性を明らかにした。

方法
膵頭十二指腸切除を行った19症例に対して、切除端の膵管からアトムチューブを挿入しインジコカルミン溶液を注入し断端からの色素の漏れの有無を調べ、切除膵の繊維化の程度と組織学的に、軽度、中等度、高度に分類し比較。

結果
血清アミラーゼ値は、術後1日目上昇し、3日目には術前値に戻っていたが、1日目の上昇は繊維化がないほど有意に高値を示した。リークテスト陽性を5例に認めたが、1例をのぞきsoft pancreas症例であった。リークテスト陽性であったsoft pancreas症例4例は全例膵液漏を生じたが、リークテスト陽性であったhard pancreas症例は膵液漏を生じなかった。

まとめ
Soft pancreasにおいては膵断端の分枝膵管からの漏れも多く、膵液漏の原因である可能性があり分枝膵管にも注意を払うべきと考えられる。