



Does Drainage Fluid Amylase Reflect Pancreatic Leakage after Pancreaticoduodenectomy?

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Abstract. This study tried to determine if drainage fluid amylase reflects pancreatic leakage after pancreaticoduodenectomy and to determine the factors affecting the drainage amylase level. Patients undergoing pancreaticoduodenectomy were recruited. The drainage amylase was measured from postoperative day (POD) 1 to POD 7. Direct evidence of pancreatic leakage was provided by upper gastrointestinal studies using a water-soluble contrast medium and methylene blue dye in the pancreaticogastrostomy group or by pancreaticography with injected contrast medium via an exteriorized pancreatic stent in the pancreaticojejunostomy group on POD 7. A total of 37 patients were recruited. The drainage amylase level was higher than the normal serum amylase (≥ 190 U/L) in more than half of the cases on the initial POD 2 specimen, with a median of 745 U/L on POD 1 and 663 U/L on POD 2. The drainage amylase level was more than three times the normal serum amylase level ($\geq 190 \times 3$ U/L) in 56.8% on POD 1, in 51.4% on POD 2, and in nearly one-third on POD 7 (29.7%). However, no pancreatic leakage occurred in any of the patients with a drainage amylase of ≥ 190 U/L. Only one case of pancreatic leakage with a small amount of drainage fluid (10 ml) and low amylase level (74 U/L), was noted. Soft pancreatic parenchyma and a nondilated pancreatic duct were significantly associated with higher drainage amylase levels. In conclusion, biochemical leakage defined by amylase-rich drainage fluid might have no clinical significance and was not necessarily clinical pancreatic leakage following pancreaticoduodenectomy.

Pancreaticoduodenectomy is considered by most to be the “weak link” during performance of pancreaticoduodenectomy. Leakage at the pancreatic anastomosis occurs in 5% to 26% of patients undergoing pancreaticoduodenectomy at major centers [1–11]. Once pancreatic leakage develops, it often contributes to significant morbidity and mortality; in fact, pancreatic leakage is the major factor most strongly linked with death in most series. Therefore efforts have been made to avoid the tragedy of pancreatic leakage. A variety of pancreatic reconstruction modifications following pancreaticoduodenectomy have been reported: end-to-side versus end-to-end, invagination versus duct-to-mucosa, pancreaticogastrostomy versus pancreaticojejunostomy, stented versus nonstented [1, 2, 12–15]. No consensus has been reached regarding one particular variation of pancreatic reconstruction being safer and less prone to leakage. There is also no universal agreement about the definition

of pancreatic leakage. Theoretically, the drainage fluid should be rich in amylase when pancreatic juice is leaked out through the pancreaticoenterostomy. Therefore, “amylase-rich” drainage has been one of the most popular definitions of pancreatic leakage used in the literature [2, 4, 5, 12–14, 16–21]. Unfortunately, the combination of different drainage amylase levels, drainage volumes, and times of measurement often makes comparison of pancreatic leakage impossible among reports. To our knowledge, there has been no study regarding the daily change of drainage amylase and correlation between the drainage amylase and pancreatic leakage after pancreaticoduodenectomy.

This prospective study was conducted to provide data for daily drainage amylase after pancreaticoduodenectomy. We tried to determine if drainage fluid amylase reflects pancreatic leakage after pancreaticoduodenectomy and to determine the factors related to the drainage amylase level.

Methods

Patients with resectable periampullary lesions were recruited into this study from July 1, 2000 to July 31, 2001. Enrolled patients were divided into two groups. One group underwent nonstented pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy (PPPD-PG). The other group underwent stented classic pancreaticoduodenectomy with pancreaticojejunostomy (CPD-PJ). The choice of surgical technique was based on the surgeons' preference. Demographic data, operating time, intraoperative blood loss, postoperative morbidity, and surgical mortality were recorded. Surgical mortality was defined as any death occurring during hospitalization or within 30 days after operation. Gastric atonia was defined as the inability to resume oral intake after postoperative day (POD) 10. The consistency of the pancreas and the diameter of the pancreatic duct were also evaluated. A pancreatic duct of more than 5 mm was considered dilated.

To observe the daily change, drainage fluid amylase from the drainage tube near the pancreatic anastomosis was measured from POD 1 to POD 7. The drainage quantity and quality were also recorded daily. To provide direct evidence of pancreatic anastomosis leakage, upper gastrointestinal studies by oral intake of 300 cc of

water-soluble contrast medium and 2 ml of methylene blue dye plus 200 ml of water in the PPPD-PG group and pancreaticography after injection of 20 ml of water-soluble contrast medium via an exteriorized pancreatic stent in the CPD-PJ group were done on POD 7. The cutoff value for normal serum amylase in our hospital was < 190 U/L. A pancreatic fistula was defined as persistent clinical pancreatic leakage for more than 7 days.

Surgical Technique

Pancreaticoduodenectomy was performed with either the pylorus-preserving modification or classic resection including antrectomy. In the nonstented PPPD-PG group, the proximal 3 to 4 cm of the pancreatic remnant was freed from the splenic vein and retroperitoneum. The pancreatic stump was anastomosed and invaginated into the mid-body posterior wall of the stomach with interrupted two-layer sutures: 3-0 silk for the outer layer placed between the pancreatic capsule and seromuscular layer of the posterior gastric wall and 3-0 polyglactin (Vicryl; Ethicon, Somerville, NJ, USA) for the outer layer placed between the cut edge of the pancreas and the full thickness of the posterior gastric wall. No pancreatic duct stent was used for the pancreaticogastrostomy. In the stented CPD-PJ group, pancreaticojejunostomy was performed by end-to-side, duct-to-mucosa, two-layer sutures using the same suture materials as were used for pancreaticogastrostomy. Two Latex closed-suction tubes were used to drain the areas near the pancreatic anastomosis. The pancreatic duct was stented by a 5F or 8F pediatric feeding tube, which was exteriorized outside the abdominal wall. After pancreatic reconstruction, an end-to-side hepaticojejunostomy and an end-to-side antecolic duodenojejunostomy or gastrojejunostomy completed the reconstruction. No vagotomy was performed in any procedure. A nasogastric tube was routinely used to decompress the stomach postoperatively, and it was removed when the gastric output from the nasogastric tube was less than 500 ml.

Statistical Analysis

Statistical analysis was carried out using SPSS 10.0 software (SPSS, Chicago, IL, USA). Data are presented as the mean \pm standard deviation (SD). Categorical variables were compared by the χ^2 test or Fisher's exact test. The independent-samples *t*-test was used to compare the means of one variable for two groups of cases, and the paired-samples *t*-test was used to compare the means of two variables for a single group. Three or more means were compared by one-way analysis of variance (ANOVA), and the least-significant difference (LSD) was used for post hoc multiple comparisons. Values of $p < 0.05$ were considered statistically significant.

Results

There were 37 patients (27 male, 10 female) undergoing pancreaticoduodenectomy for resectable periampullary lesions. The average age was 65.5 ± 15.6 years (median 69 years, range 14–89 years). The primary lesions included 14 ampulla of Vater cancers, 13 pancreatic head cancers, 1 duodenal cancer, 1 duodenal leiomyosarcoma, 1 distal common bile duct cancer, 2 endocrine tumors, 1 ampullary villous adenoma, 1 pancreatic microcystic adenoma, 2 cases of chronic pancreatitis, and 1 colon cancer with duodenal and pancreatic invasion. PPPD-PG was performed in 27 patients and CPD-PJ

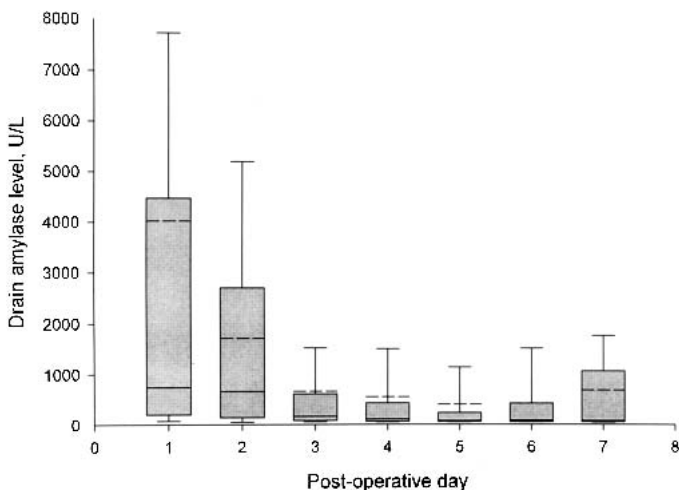


Fig. 1. Box plot shows 25th/75th percentile boxes and 10th/90th percentile whiskers below and above each box for postoperative drainage fluid amylase. The short solid line in each box marks the median, and the short dashed line marks the mean. Postoperative day 1 drainage fluid amylase was significantly higher than that on other postoperative days.

in 10. The mean operating time was 7.0 ± 1.9 hours (6.4 ± 1.6 hours for PPPD-PG and 8.5 ± 2.0 hours for CPD-PJ), with a median of 7.0 hours (6.5 hours for PPPD-PG and 7.8 hours for CPD-PJ) and a range of 3.5 to 12.5 hours (3.5–11.5 hours for PPPD-PG and 6.5–12.5 hours for CPD-PJ). The mean intraoperative blood loss was 748.3 ± 380.5 ml (768.9 ± 385.3 ml for PPPD-PG and 688.9 ± 382.2 ml for CPD-PJ), with a median of 700 ml (750 ml for PPPD-PG and 700 ml for CPD-PJ) and a range of 150 to 2000 ml (200–2000 ml for PPPD-PG and 150–1300 ml for CPD-PJ).

The drainage fluid amylase was highest on POD 1 and was significantly higher than levels on other postoperative days. As shown in Figure 1 and Table 1, the drainage fluid amylase was higher than the normal serum amylase (≥ 190 U/L) in most cases on the initial POD 2, with a median of 745 U/L (range 43–66,079 U/L) on POD 1 and a median of 663 U/L (range 25–9036 U/L) on POD 2. The drainage fluid amylase was more than three times the normal serum amylase ($\geq 190 \times 3$ U/L) in more than half of the cases on POD 1 (56.8%) and POD 2 (51.4%). On POD 7 the median drainage fluid amylase was 74 U/L but ranged from 21 to 7130 U/L, with 35.1% ≥ 190 U/L, 29.7% $\geq 190 \times 2$ U/L, and 29.7% $\geq 190 \times 3$ U/L. However, the drainage did not become pus-like from POD 1 to POD 7, and pancreatic leakage did not occur in any case with the drainage fluid amylase equal to or more than the normal serum amylase (≥ 190 U/L), studied by upper gastrointestinal roentgenogram with contrast medium and oral intake of methylene blue dye in the PPPD-PG group or pancreaticography with injection of contrast medium via an exteriorized pancreatic stent in the CPD-PJ group on POD 7.

The pancreatic parenchyma was soft in 23 (62.2%) patients. The drainage fluid amylase was significantly higher in the group with soft pancreatic parenchyma than in the group with fibrotic pancreatic parenchyma for each day during the study period (Table 2). The pancreatic duct was small (≤ 5 mm) in 20 (54.1%) patients. There was a tendency for patients with a small pancreatic duct to have higher drainage fluid amylase levels. The difference in drainage fluid amylase between the nondilated and dilated groups reached statistical significance on PODs 2, 3, 5, 6, and 7 (Table 3).

Table 1. Drainage fluid amylase level and drainage amount after pancreaticoduodenectomy.

Time of sample	Amylase conc. (U/L)	Percent of cases at various drainage amylase concentrations			Drainage amount (ml)
		≥ 190 U/L ^a	≥ 190 × 2 U/L	≥ 190 × 3 U/L	
POD 1*					
Median (range)	745 (43–66,079)	75.5	62.2	56.8	105 (20–370)
Mean ± SD	4030 ± 11,012				137 ± 94
POD 2					
Median (range)	663 (25–9036)	64.9	54.1	51.4	120 (20–406)
Mean ± SD	1715 ± 2396				134 ± 96
POD 3					
Median (range)	161 (28–5950)	48.6	35.1	24.3	80 (10–450)
Mean ± SD	666 ± 1199				114 ± 107
POD 4					
Median (range)	107 (25–8041)	35.1	29.7	16.2	60 (5–530)
Mean ± SD	552 ± 1369				107 ± 102
POD 5					
Median (range)	75 (27–3761)	27.0	18.9	16.2	85 (3–540)
Mean ± SD	401 ± 828				102 ± 96
POD 6					
Median (range)	84 (46–3730)	35.1	27.0	21.6	50 (5–720)
Mean ± SD	425 ± 747				98 ± 138
POD 7					
Median (range)	74 (21–7130)	35.1	29.7	29.7	40 (5–450)
Mean ± SD	687 ± 1344				64 ± 78

POD: postoperative day; conc.: concentration.

^aThe cutoff value for normal serum amylase in our hospital was < 190 U/L.

*POD day 1 drainage amylase was significantly higher than that on other PODs by one-way analysis of variance and post hoc multiple comparisons (least significant difference).

Table 2. Drainage fluid amylase and consistency of pancreatic parenchyma after pancreaticoduodenectomy.

Time of sample	Amylase (U/L) by consistency of pancreatic parenchyma		p
	Soft (n = 23)	Fibrotic (n = 14)	
POD 1			
Median (range)	3270 (129–66,079)	170 (43–745)	0.041
Mean ± SD	6356 ± 13,545	208 ± 197	
POD 2			
Median (range)	1446 (37–9036)	129 (25–893)	0.000
Mean ± SD	2637 ± 2649	201 ± 240	
POD 3			
Median (range)	371 (28–5950)	76 (35–480)	0.009
Mean ± SD	991 ± 1431	131 ± 149	
POD 4			
Median (range)	332 (25–8041)	59 (42–137)	0.038
Mean ± SD	845 ± 1682	70 ± 29	
POD 5			
Median (range)	179 (27–3761)	58 (40–97)	0.016
Mean ± SD	607 ± 1002	62 ± 17	
POD 6			
Median (range)	274 (47–3730)	58 (46–291)	0.006
Mean ± SD	637 ± 888	77 ± 63	
POD 7			
Median (range)	289 (21–7130)	52 (23–74)	0.006
Mean ± SD	1071 ± 1595	55 ± 17	

Table 3. Drainage fluid amylase and pancreatic duct after pancreaticoduodenectomy.

Time of sample	Drainage fluid amylase conc. (U/L)		p
	Pancreatic duct ≤ 5 mm (n = 20)	Pancreatic duct > 5 mm (n = 17)	
POD 1			
Median (range)	3725 (199–66,079)	184 (43–7610)	0.084
Mean ± SD	6762 ± 4486	815 ± 1825	
POD 2			
Median (range)	1378 (141–9036)	131 (25–4990)	0.007
Mean ± SD	2638 ± 2741	630 ± 1296	
POD 3			
Median (range)	426 (72–5950)	86 (28–1274)	0.026
Mean ± SD	1049 ± 1518	214 ± 316	
POD 4			
Median (range)	230 (43–8041)	69 (25–2180)	0.169
Mean ± SD	824 ± 1777	232 ± 514	
POD 5			
Median (range)	158 (53–3761)	60 (27–902)	0.045
Mean ± SD	639 ± 1064	120 ± 209	
POD 6			
Median (range)	280 (47–3730)	55 (46–464)	0.009
Mean ± SD	703 ± 933	98 ± 110	
POD 7			
Median (range)	621 (42–7130)	51 (21–785)	0.011
Mean ± SD	1174 ± 1687	113 ± 184	

Table 4 shows the surgical morbidity and mortality after pancreaticoduodenectomy. Complications occurred in 15 (40.5%) patients: 11 (40.7%) in the PPPD-PG group and 4 (40.0%) in the CPD-PJ group. The complication rates were not significantly different between the PPPD-PG and CPD-PJ groups. The most common complication was gastric atonia, occurring in 5 (13.4%) patients, all of whom (18.5%) were in the PPPD-PG group. One case of pancreatic leakage was noted in the CPD-PJ group, which was

proved by pancreaticography after injection of 20 ml water-soluble contrast medium via an exteriorized pancreatic stent on POD 7. For the patient with pancreatic leakage, the drainage suddenly became pus-like on POD 7, but the drainage fluid amylase was only 74 U/L and the drainage amount was 10 ml. The pancreatic leakage was managed by a tube drain with suction, which eventually did well. An intraabdominal abscess resulted from drainage tract infection in two PPPD-PG patients and in one CPD-PJ patient and from

Table 4. Surgical morbidity and mortality after pancreaticoduodenectomy.

Parameter	Total (n = 37)	PPPD-PG (n = 27)	CPD-PJ (n = 10)	p
Patients with morbidity	15 (40.5%)	11 (40.7%)	4 (40%)	1.000
Gastric atonia	5 (13.5%)	5 (18.5%)	0	0.295
Intraabdominal abscess	4 (10.8%)	2 (7.4%)	2 (20%)	0.291
Wound infection	4 (10.8%)	2 (7.4%)	2 (20%)	0.291
Upper gastrointestinal bleeding	2 (5.4%)	2 (7.4%)	0	1.000
Intraabdominal bleeding	1 (2.7%)	1 (3.7%)	0	1.000
Pancreatic leakage	1 (2.7%)	0	1 (10%)	1.000
Pneumonia	1 (2.7%)	1 (3.7%)	0	1.000
Sepsis	1 (2.7%)	1 (3.7%)	0	1.000
Mortality	1 (2.7%)	1 (3.7%)	0	1.000

PPPD-PG: pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy; CPD-PJ: classic pancreaticoduodenectomy with pancreaticojejunostomy.

pancreatic leakage in one CPD-PJ patient. Sepsis in one PPPD-PG patient was due to pneumonia. One (2.7%) patient died of massive small bowel bleeding without known underlying pathology 105 days after operation.

Discussion

Pancreatic leakage has been the major concern when performing pancreaticoduodenectomy. Many factors, including soft pancreatic texture, ampullary or duodenal lesions, long operating time, intraoperative blood transfusion, and low surgical volume were found by univariate analysis to increase significantly the risk of pancreatic fistula formation [2, 6]. Nevertheless, surgical technique still plays a crucial role in preventing pancreatic leakage. Currently, biochemical study of the drainage fluid amylase level is one of the most popular methods for reporting pancreatic leakage in the literature. There are various biochemical definitions of pancreatic leakage, such as drainage of ≥ 50 ml amylase-rich fluid on or after POD 10 [2, 4], drainage of ≥ 50 ml amylase-rich fluid (more than three times the normal plasma level) on or after POD 7 [5, 12, 19], drainage of more than 50 ml with the amylase level more than twice the serum amylase value [6], drainage of more than 1000 U/L of amylase-rich fluid on or after POD 7 [13], drainage with an amylase level of more than 10,000 U/L [14], drainage of more than 30 ml amylase-rich fluid on or after POD 7 or the continued use of an intraoperatively placed drain at the time of discharge regardless of the postoperative day or amount [16], drainage of more than 30 ml amylase-rich fluid (> 5000 U/L) for more than 10 days [17], drainage of more than 50 ml amylase-rich fluid ($> 10,000$ U/L) for more than 10 days [18], a drain amylase level more than three times the serum amylase value on the first day of feeding [20]. Without a universal definition that truly reflects pancreatic leakage, the leakage rate of a pancreaticoenterostomy may be misinterpreted and cannot be compared with others.

Our study demonstrated that elevation of drainage fluid amylase was not unusual following pancreaticoduodenectomy, especially during the initial two postoperative days. More than half of the cases on POD 1 (56.8%) and POD 2 (51.4%) had a drainage fluid amylase level of $\geq 190 \times 3$ U/L (three times the normal serum amylase). On POD 7 about one-third of the cases still had an elevated drainage fluid amylase level ($35.1\% \geq 190$ U/L, $29.7\% \geq$

190×2 U/L, $29.7\% \geq 190 \times 3$ U/L). However, the drainage fluid did not become pus-like throughout the study period, and pancreatic leakage did not occur in any case with elevated drainage fluid amylase (≥ 190 U/L), confirmed by roentgenograms with contrast medium and methylene blue dye. On the other hand, the drainage fluid suddenly turned pus-like in the CPD-PJ case, with pancreatic leakage proved by pancreaticography with contrast medium on POD 7, but the drainage amylase remained low (74 U/L) and the drainage amount was small (10 ml). Obviously, the drainage fluid amylase level does not necessarily reflect pancreatic leakage following pancreaticoduodenectomy, as shown in this study.

By our analysis, soft pancreatic parenchyma and a small pancreatic duct are significantly associated with higher drainage amylase levels compared to fibrotic pancreatic parenchyma and a dilated pancreatic duct. This finding suggests that the texture of the pancreas may play a role in the drainage fluid amylase level following pancreaticoduodenectomy. Based on the above observations, we inferred that the pancreatic remnant after pancreaticoduodenectomy might become a “sweating” gland that releases amylase-rich exudate, similar to the pancreatic ascites seen with acute pancreatitis. This inference could explain why the amylase-rich drainage fluid did not necessarily reflect the clinical pancreatic leakage following pancreaticoduodenectomy and also why the drainage fluid amylase was higher in patients with a relatively normal pancreas than in those with a fibrotic, atrophic pancreas.

Conclusions

Biochemical leakage defined by the amylase-rich drainage fluid level may have no clinical significance and was not necessarily the clinical pancreatic leakage following pancreaticoduodenectomy. We recommended that assessment of pancreatic leakage be based on persistent pus-like drainage and confirmed by roentgenography with a contrast medium or dye such as methylene blue in the drainage fluid.

Résumé. Le but de cette étude a été de clarifier si le taux d'amylase dans le liquide de drainage peut prédire une fistule pancréatique après duodéno pancréatectomie et de déterminer les facteurs qui agissent sur le taux d'amylase dans ce liquide. On a mesuré, dans le liquide de drainage des patients ayant eu une duodéno pancréatectomie, le taux d'amylase entre les jours postopératoires 1 à 7. La preuve directe d'une fistule pancréatique a été obtenue au septième jour postopératoire par une fistulographie aux hydrosolubles et/ou par une épreuve au bleu de méthylène dans le groupe de patients ayant eu une anastomose pancréatogastrique, ou par injection de produit de contraste via le drain interne pancréatique dans le groupe d'anastomose pancréatojejunale. Il y avait 37 patients inclus dans l'étude. Pendant les deux premiers jours postopératoires, le taux d'amylase dans le liquide était plus élevé que le taux normal dans le sérum (≥ 190 U/L) chez plus de la moitié des patients, avec une médiane de 745 U/L au premier jour postopératoire et de 663 U/L au deuxième jour postopératoire. Le taux d'amylase dans le liquide du drainage était supérieur à trois fois le taux normal dans le sérum ($\geq 190 \times 3$ U/L) chez 56.8% des patients au premier jour postopératoire, chez 51.4% des patients au deuxième jour postopératoire et chez presque un tiers des patients au septième jour postopératoire (29.7%). Cependant, aucune fistule pancréatique n'a été détectée par la suite chez les patients dont le contenu en amylase dans le drain était ≥ 190 U/L. Seul un cas de fistule, à bas débit (10 mL) avec un taux peu élevé d'amylase (74 U/L), a été noté. Ont été significativement associés à un taux élevé d'amylase dans le drain, un parenchyme pancréatique mou et un canal de Wirsung non dilaté. En conclusion, après duodéno pancréatectomie céphalique, il se peut qu'une fistule “biochimique,” définie par un taux élevé d'amylase dans le liquide de drainage, n'ait aucune signification clinique et ne traduise pas forcément une fistule pancréatique clinique.

Resumen. Determinar si la cifra de amilasa obtenida por el drenaje guarda relación con una fuga anastomótica tras duodenopancreatectomía y averiguar que factores pueden influir en los niveles de amilasa obtenidos por el drenaje. Se estudiaron pacientes duodenopancreatectomizados, valorándose los niveles de amilasa del líquido drenado desde el primero al séptimo día del periodo postoperatorio. Para el diagnóstico de fuga anastomótica se utilizaron en el grupo con anastomosis pancreatogástrica estudios radiográficos de tracto digestivo alto con un medio de contraste soluble en agua y también con azul de metileno. En el grupo de pacientes en que el remanente pancreático se anastomosó al yeyuno, se instiló al séptimo día del postoperatorio a través de una endoprótesis exteriorizada del páncreas, un medio de contraste para obtener una pancreatografía. Se estudiaron 37 pacientes. Durante los dos primeros días del postoperatorio, la amilasa del líquido de drenaje fue, en más del 50% de los casos, superior a la amilasemia normal (≥ 190 U/L), alcanzando el primer día una media de 745 U/L y en el 2º 663 U/L. En el 56.8% de los pacientes la cifra de amilasa obtenida del drenaje al primer día fue 3 veces superior a la amilasemia normal ($\geq 190 \times 3$ U/L). Cifras semejantes se constataron en el 51.4% de los pacientes al 2º día del postoperatorio y en el 29.7% al séptimo día. Sin embargo, no se registró fuga anastomótica alguna en ninguno de los casos en los que la amilasa obtenida en el líquido de drenaje fue superior a 190 U/L. Sólo se observó una fuga anastomótica en un paciente con débito bajo (10 ml) por el drenaje y cifras de amilasa de 74 U/L. Páncreas de consistencia blanda y sin dilatación del Wirsung se acompañaron de cifras más elevadas de amilasa en el líquido drenado. Tras una duodenopancreatectomía la fuga bioquímica definida por amilasa alta en el líquido de drenaje no tiene significación clínica alguna.

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