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Acute pancreatitis after liver transplantation: incidence and contributing factors

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Abstract In order to assess the incidence and possible predisposing and contributing factors in the development of acute pancreatitis after liver transplantation, we reviewed the medical records of all 1832 adult patients who underwent 2161 orthotopic liver transplantation (OLTx) procedures in our center between January 1987 and September 1992. Of these patients, 55 (3 % incidence) developed clinical pancreatitis and 247 (13.4 % incidence) developed hyperamylasemia (biochemical pancreatitis). Overall mortality in cases of clinical pancreatitis was 63.6 %. The mortality in cases of hyperamylasemia was similar to that found in the general liver transplant population (i.e., 23 %). A strong correlation was found between pancreatitis after liver transplantation and end-stage liver disease due to hepatitis B (30 % of the cases, $P = 0.00001$). Extensive surgical dissection around the pancreas ($P < 0.05$), the type of biliary reconstruction following liver transplantation ($P < 0.05$), and the number of liver grafts received by the same patient ($P = 0.00001$) appeared to be possible contributing factors as did the duration of veno-venous bypass and the quantity of IV calcium chloride administered intraoperatively.

Key words Pancreatitis · Liver transplantation

Introduction

Pancreatitis constitutes one of the most severe complications following liver transplantation. In the general population, it has been postulated that ischemia [38], drugs (i.e., steroids [3, 5, 23, 31], furosemide [7, 15, 39], unidentified viral infections [2, 4], postoperative hyperparathyroidism, vasculitis, calcium chloride administration [21, 29, 36], and intraoperative trauma may all be contributing factors. Alexander et al. [1] reported a high incidence of post-OLTx (orthotopic liver transplantation) pancreatitis in patients suffering from hepatitis B. In fact, a report from the same institution revealed the magnitude of the problem and raised questions for further study [26]. To gain further insight into this problem, a retrospective analysis of the incidence of post-OLTx pancreatitis was undertaken. A main objective was to identify the variables most strongly associated with pancreatitis after OLTx.

Materials and methods

From 1 January 1987 to 30 September 1992, 1832 patients underwent 2161 OLTx procedures at the Presbyterian University Hospital of Pittsburgh. Of these patients, 302 developed postoperative hyperamylasemia, and all of their records were reviewed. This report deals with post-OLTx pancreatitis in the immediate postoperative period (up to 30 days after OLTx). In fact, most of these patients developed this complication during the 1st postoperative week, and mostly in the intensive care unit (ICU). Apart from he-

patitis B-positive serology, which has been shown to predispose patients to the development of pancreatitis, no other preoperative contributing condition was identified. For the purpose of this study, patients with hyperamylasemia who had serum creatinine above 2 mg were excluded, since measurements of creatinine and amylase clearance were lacking.

Amylase was determined every other day in the immediate posttransplant period or more frequently when indicated. Serum amylase measurements were performed using the Kodak Enzymatic Amylase Kit (Eastman Kodak, Rochester, N.Y.).

Clinical pancreatitis was defined as an elevation of the serum amylase level in excess of twice the value of the normal upper limit, plus any additional diagnostic CT scan findings (such as pancreatic enlargement or pseudocyst/abscess formation), intraoperative findings, or autopsy confirmation. Clinical findings were not considered because they were ill-defined. Patients diagnosed as having clinical pancreatitis were immediately brought to the ICU postoperatively; most of them were on mechanical ventilation. Patients whose amylase levels were elevated to more than twice the normal upper limit, at least in one measurement, were defined as having hyperamylasemia (biochemical pancreatitis). This term was first used by Alexander et al. [1], and we used it for all patients with hyperamylasemia who lacked the clinical or CT findings consistent with pancreatitis. Of course, the use of creatinine clearance values in the assessment of renal function is more reliable than that of serum creatinine levels. However, we chose to use the 2-mg serum creatinine threshold, based on the above-mentioned reference by Alexander et al. Moreover, in this retrospective study, it was not feasible to obtain creatinine clearance values for all of our patients.

All the patients who developed clinical pancreatitis wee put on either double or single venovenous bypass. Double bypass is considered when the femoral and portal veins are brought together to a centripetal pump (Bio-Medicus, Minnetonka, Minn.) and the return flow is connected to the axillary vein. Single bypass was the choice in cases of previous portocaval shunts or portal vein thrombosis or when the portal vein was unsuitable for double bypass. The liver grafts were harvested according to the technique described by Starzl et al. [33].

From 1987 until 1989 cyclosporin (CyA) plus steroids was the standard immunosuppressive treatment for liver recipients. For rejection episodes a bolus dose of steroids was administered intravenously, followed by a steroid recycling protocol. If there was no response, a course of OKT3 was given intravenously. Starting in 1989, FK 506 replaced CyA in the protocols used, and the steroid doses were significantly lowered because of the greater FK 506 potency. The antirejection treatment remained unchanged. Until bowel function had resumed, lipids in the form of total parenteral nutrition (TPN) were administered as a postoperative rule. No difference was found regarding the incidence or severity of pancreatitis between groups of patients treated with CyA and those treated with FK 506. In all patients undergoing surgical treatment, intraabdominal sepsis was documented preoperatively.

Neither Ranson score nor other criteria were used to assess the severity of pancreatitis, since most of these are greatly deranged following liver transplantation. The therapeutic choice was based mostly on the abdominal CT findings. Furthermore, in most of the cases dynamic CT pancreatography was carried out in order to assess the extent of the necrosis.

Treatment of clinical pancreatitis was either medical or surgical. Surgical treatment included simple drainage, debridement, or pancreatectomy.

Statistical analysis was performed using Student's t-test for unpaired samples. The chi-square method was used to evaluate the association and the differences in proportions. A P value below 0.05 was considered to be significant.

Results

Of the 1832 patients who were studied, 302 (16.4 %) developed hyperamylasemia during the postoperative course of OLTx without renal insufficiency (serum creatinine < 2 mg %). Of these, 55 (3 %) developed clinical pancreatitis; in the other 247 patients, amylase levels eventually returned to normal.

Of the 55 patients who developed clinical pancreatitis, 17 (30.9 %) had been transplanted because of hepatitis B cirrhosis, as compared to 114 (6.2 %) of the total number of liver transplant recipients who had been transplanted for the same reason. Fifteen patients who later developed clinical pancreatitis (27.3 %) had been transplanted for hepatitis non-A non-B cirrhosis, as against 340 (18.6 %) of the total number of liver transplant recipients. Eight patients (14.5 %) versus 172 patients (9.4 %) had been transplanted for primary biliary cirrhosis, while 7 (12.7 %) versus 310 (16.9 %) had been transplanted for alcoholic cirrhosis. Three patients (5.4 %) versus six (0.3 %) had been transplanted for fulminant hepatic failure related to drug overdose. Two patients (3.6 %) versus 129 (7.0 %) had been transplanted for primary sclerosing cholangitis. Two patients (3.6 %) versus 82 (4.5 %) had been transplanted for hepatocellular carcinoma. Finally, 1 patient who developed clinical pancreatitis (1.8 %) versus 59 (3.2 %) of the total number of liver transplant recipients had been transplanted for autoimmune hepatitis (Fig. 1). This distribution of diseases necessitating OLTx among patients who later developed clinical pancreatitis was statistically highly significant ($P = 0.00001$) compared with the distribution among all liver transplant recipients.

Of the 55 patients with clinical pancreatitis, 40 (72.7 %) had received FK 506 plus steroids as immunosuppressive treatment, and 15 (27.2 %) had received CyA plus steroids. All of the patients had also been treated with furosemide.

The annual distribution of these 55 cases of post-OLTx pancreatitis was: 8 patients (14.5 %) for the year 1987, 5 patients (9 %) for the year 1988, 12 patients (21.8 %) for the year 1989, 12 ptients (21.8 %) for the year 1990, 13 patients (23.6 %) for the year 1991, and 5 patients (9 %) for the first 9 months of 1992. This distribution is not statistically significant compared to the annual distribution of OLTx procedures for the entire liver transplant population during the same time period (Table 1). The mean age of these 55 patients was 47.1 years (SD ± 14.2), with a range between 20 and 69 years. The mean age of all liver transplant patients was 47.0 years (SD ± 12.7). The difference between the two groups is not statistically significant. The distribution according to age groups is shown in Fig. 2.

Twenty-nine (52.7 %) of the 55 patients who developed post-OLTx pancreatitis had received primary liver grafts. Twenty patients (36.3 %) developed pancrea-

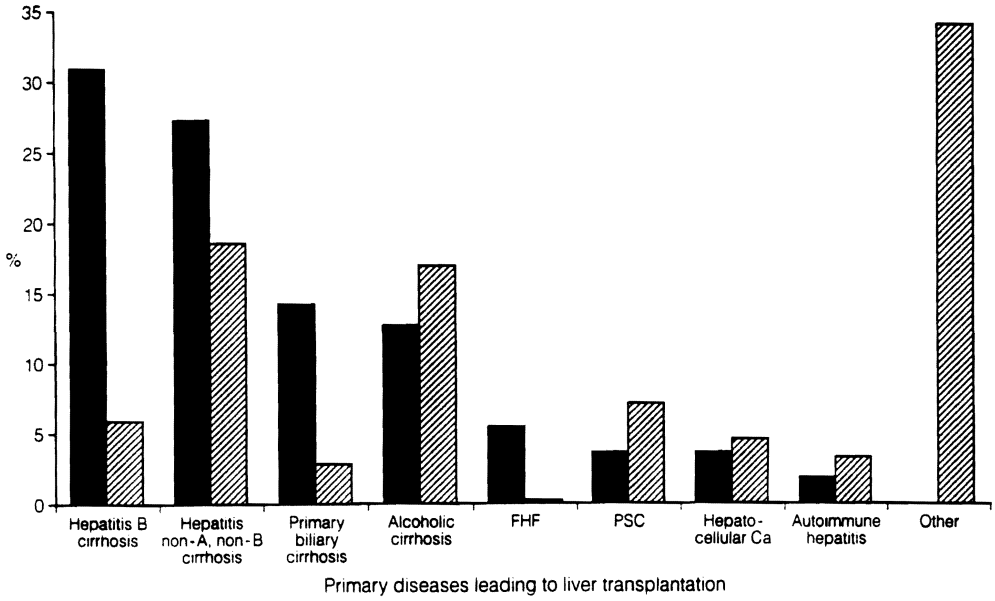

Fig. 1 Distribution of primary diseases leading to liver transplantation in the group of patients who developed clinical pancreatitis (■; $n = 55$) and in the total number of liver transplant recipients (▨ $n = 1832$). $P < 0.01$ (Hep hepatitis, FHF fulminant hepatic failure, PSC, primary sclerosing cholangitis)

Table 1 Patient data

Age (years)	Sex	History of alcoholism	Type of transplants in pancreatitis group ($n = 55$)	No. of transplants followed by pancreatitis per year ($n = 55$)
Mean 47.1	M 33 (60%)	Yes 12 (21.8%)	1st 29 (52.7%)	1987 8 (14.5%)
SD ± 14.2	F 22 (40%)	No 43 (79.1%)	2nd 20 (36.3%)	1988 5 (9.09%)
Range 20–69	Ratio M: F 1.5: 1		3rd 6 (10.2%)	1989 12 (21.8%)
			> 3rd 0 (0%)	1990 12 (21.8%)
				1991 13 (23.6%)
				1992[a] 5 (9.09%)
P = NS	P = NS		$P = 0.00001$	P = NS

[a] First 9 months

titis after receiving their second liver graft, and 6 patients (10.2%), after they had received their third liver transplant. Statistically, this proved to by highly significant since, during the same time period, 72% of the total number of liver transplants were primary grafts ($P = 0.00001$; Table 1; Fig. 3).

The postoperative day (POD) on which hyperamylasemia developed was on the average POD 2.2 (SD ± 1.9); it ranged from the day of transplantation to POD 10. The diagnosis of clinical pancreatitis, which was confirmed either by CT scan (enlargement of the pancreas, pseudocyst, abscess) or during the operation or at autopsy, was established on mean POD 4.7 (SD ± 3); this ranged from POD 1 to POD 11 (Table 2).

All 55 patients had a venovenous bypass, either double or single; the mean duration was 98.1 min (SD ± 29), the range 45–198 min. Twenty-nine patients (52.7%) were on bypass for less than 1 h 30 min; 26 patients (47.2%) were on bypass beyond this limit (Table 2).

Regarding the biliary reconstruction, 40 patients (72.7%) had a Roux-en-Y stented choledochojejunostomy and 15 patients (27.2%) had a donor-recipient duct-to-duct anastomosis over a T tube. This distribution is statistically significant ($P < 0.05$) compared with the total number of liver transplant recipients in whom only 52% of the biliary reconstructions were performed in a Roux-en-Y fashion (Table 2).

Portal vein thrombosis was identified in 10 patients (18.1%), 4 of whom (7.2%) had a thrombectomy and 6 (10.9%), a venous graft. Of the 6 who received grafts, 4 had interposition grafts and 2, jump grafts from the superior mesenteric vein to portal vein (Table 2). In the general liver transplant population, a portal venous graft was used in approximately 2.85% of the cases ($P < 0.002$).

The frequency of an arterial graft from the infrarenal aorta (brought either anteriorly or posteriorly to the pancreas) to the donor hepatic artery was high, and this occurred in 24 patients (43.6%; Table 2). In the general

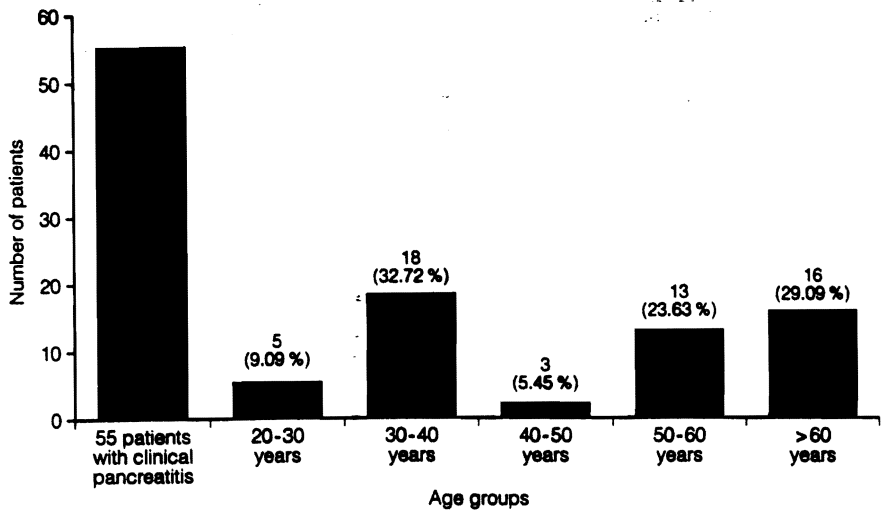

Fig. 2 Distribution of post-OLTx pancreatitis cases ($n = 55$) in different age groups

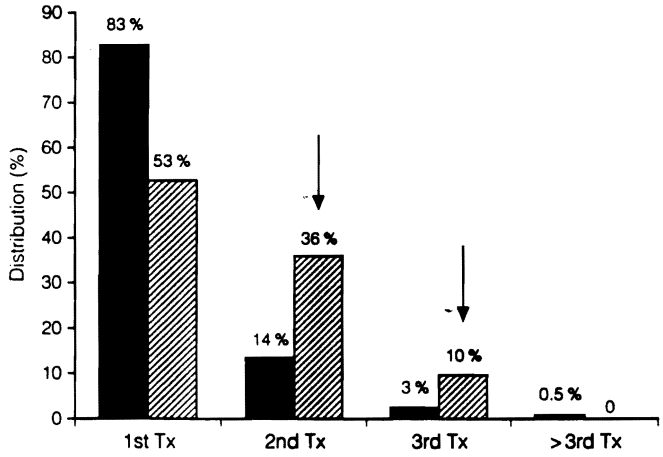

Fig. 3 Distribution of transplants (Tx) in the group of patients who developed clinical pancreatitis (▨) and in the total number of liver transplant recipients (■) $P = 0.00001$

liver transplant population, the overall incidence of the use of an arterial graft for the reperfusion of the liver allograft was 17 % during the same period ($P < 0.001$). Splenectomy at the time of the OLTx was carried out in 2 patients (3.6 %), and ligation of the celiac axis was performed in another two patients (3.6 %). Dissection of the region of the splenic artery or the celiac axis was carried out in a (16.3 %) and 8 (10.9 %) patients, respectively.

The use of lipids in the TPN solution was consistent for all patients. The mean duration was 4.5 days (SD ± 3.4) and the range 1–20 days postoperatively or until the time pancreatitis developed.

Thirty-six of the 55 patients (65.4 %) received medical treatment and the other 19 (34.5 %) underwent surgical treatment. Depending on the operative findings, surgical treatment consisted in simple drainage, open abdomen, or pancreatectomy. Three patients were treated by regional pancreatectomy: 2 of them died and 1 survived (Table 2). Sixteen patients (29 %) presently remain well with the graft they had at the time pancreatitis developed; all of these patients received medicamentous treatment. Four patients (7.2 %) remain well with another graft that was transplanted during or after the episode of pancreatitis; of these, 2 received medical and the other 2 surgical treatment. Overall mortality was 63.6 % (35 patients). The mortality among the surgically treated patients was 89 % (17 patients), whereas 50 % of the medically treated patients survived this complication (Fig. 4).

Discussion

The incidence of pancreatitis after OLTx depends on the criteria used to define this complication. Proven pancreatitis, confirmed by evidence obtained from CT scan, operation, or autopsy, has been reported to vary between 0.12 % and 17 % following renal transplantation [8, 10, 14, 25, 28, 35] and cardiac surgery [18, 24, 26, 29, 34] and has been associated with high mortality rates ranging between 20 % and 70 % [8, 10, 14, 25, 28, 35]. The above data are consistent with our findings concerning the incidence of pancreatitis, which was 3 % among the total number of liver transplant recipients; the mortality rate was 63.6 %. The incidence of biochemical pancreatitis, which was 16.4 %, did not appear to agree with the higher figures observed following cardiac surgery [16, 24, 26, 29, 34].

In our study we found that several factors contributed to the incidence of post-OLTx acute pancreatitis. Noteworthy among our observations was the high incidence of hepatitis B cirrhosis as a liver disease that leads to liver transplantation. One third of the patients

Table 2 Clinical data (*retx* retransplantation)

Postoperative day on which hyperamylasemia started	Postoperative day on which clinical pancreatitis was diagnosed	Use of veno-venous bypass (min)	Type of biliary reconstruction*	Use of arterial graft**	Portal vein thrombosis***	Intraoperative i.v. $CaCl_2$	Treatment and outcome
Mean 2.2	Mean 4.7	Mean 98.1	Duct-to-duct 15 (27.2 %)	Yes 24 (43.6 %)	Patients 10 (18.1 %)	Mean 7.9	Surgical 19 (34.5 %)
SD ± 1.9	SD ± 3	SD ± 29	Roux-en-Y 40 (72.7 %)	No 31 (56.3 %)	Thrombectomy 4 (7.2 %)	SD ± 3.4	Medical 36 (65.4 %)
Range 0–10	Range 1–11	Range 45–198			Venous graft 6 (10.9 %)	Range 2.5–20	
							Death 35 (63.6 %)
							Well+retx[a] 4 (7.2 %)
							Well-retx[b] 16 (29 %)

* $P < 0.05$
** $P < 0.01$
*** $P < 0.002$

[a] Patients who survived the episode but needed retransplantation
[b] Patients who survived the episode with original transplant

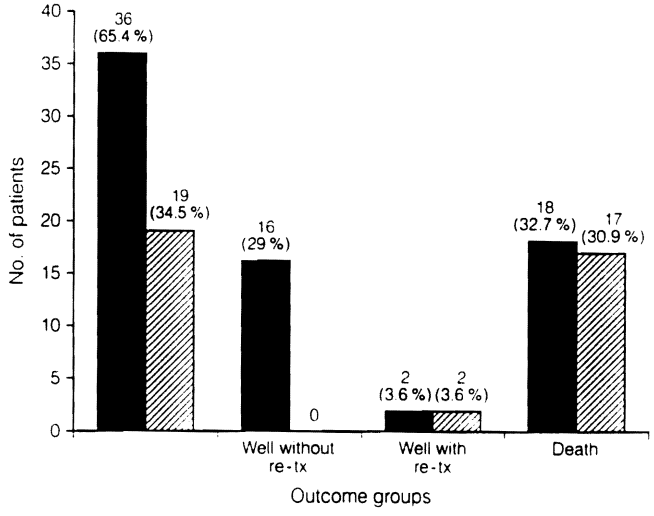

Fig. 4 Relation between kind of treatment and outcome (■ medical, ▨ surgical treatment)

who developed post-OLTx pancreatitis were in this group of patients. This finding is particularly significant and is consistent with the view of Alexander et al. [1].

The distribution of pancreatitis cases among age groups (Fig. 2) was found to be high in the third decade of life; this declined in the fourth decade and rose again in the fifth and the sixth decades. This is a very important observation, because this severe and possibly lethal complication occurs with a relatively high incidence in the 30- to 40-year age group.

Another interesting observation was that 36.3 % of the patients had already received their second liver transplant when pancreatitis developed (Fig. 3). A possible explanation for this could be the magnitude of the peripancreatic dissection that is necessary when the patient undergoes OLTx for the second or third time ($P = 0.00001$).

All of the 55 patients were on venovenous bypass during the OLTx operations, and of these 47.2 % were on bypass for more than the average duration of 90 min. There is a statistically significant difference between this group and the group that was on bypass for less than 90 min ($P < 0.05$). This is consistent with the knowledge that extracorporeal bypass causes ischemia and subsequent injury to the pancreas as a result of the hypotension and low cardiac output that is observed during bypass and that is strongly related to the duration of the bypass [17, 22, 27, 30, 32, 38].

Furthermore, it is very significant that 40 patients (72.7 %) had their biliary reconstruction in the form of the donor bile duct to a recipient Roux-en-Y loop. This high proportion seems to be an important contributing factor for the occurrence of pancreatitis. We observed a higher incidence of portal vein thrombosis (18.1 %) in the pancreatitis group. This is probably related to the dissection and unavoidable surgical manipulations in the peripancreatic region during the thrombectomy and to the need for a venous jump graft construction.

A strong correlation was found between the high incidence (43.6 %) of the construction of an arterial graft in the pancreatitis group and the subsequent development of post-OLTx pancreatitis. The extensive peripancreatic dissection that is necessary when an arterial graft is to be constructed appears to be an important contributing factor. This may also be true in cases where ligation or dissection of the celiac axis is carried out. It is well known that these surgical manipulations cause me-

chanical trauma in the peripancreatic region. The incidence of pancreatitis in relation to the two immunosuppressive regimens that were used – either FK 506 plus steroids or CyA plus steroids – was of no statistical significance. Therefore, since FK 506 replaced CyA starting in 1989, it can be assumed that the pancreatitis distribution was not higher with either immunosuppressive agent. This finding reversed the initial hope that the introduction of the FK 506 would lower the incidence of post-OLTx pancreatitis, since it allows for the use of lower doses of steroids.

It is also noteworthy that all of the patients were receiving large doses of furosemide, which like steroids, is well known to be associated with pancreatitis [3, 5, 7, 15, 23, 31, 39].

Among the factors associated with post-OLTx pancreatitis was the intraoperative administration of calcium chloride. The risk of pancreatitis induced by calcium chloride is dose related. Although even a close correlation such as this cannot confirm a cause-and-effect relation, there is strong evidence from earlier clinical and experimental studies that there is a link between hypercalcemia and pancreatitis [6, 9, 11–13, 17, 19, 20, 37]. These studies have shown that the administration of large doses of calcium chloride may contribute to the development of pancreatic cellular injury. The risk increases rapidly when the dose is more than 1.5 g. Thus, in an attempt to reduce the incidence of pancreatic injury and, ultimately, of severe pancreatitis, it seems prudent to limit the dose of calcium chloride to 1.5 g in the absence of documentation of abnormally low levels of ionized calcium. Our observations are in agreement with these results, since all of our patients with post-OLTx pancreatitis had, in fact, received more than 1.5 g of calcium chloride intraoperatively.

Lipids did not appear to play an important role as a predisposing factor in the development of post-OLTx pancreatitis, since lipids are administered to all of our transplant patients in the TPN solutions during the immediate postoperative period.

The mortality rate proved to be very high (63.6%). The higher mortality rate in patients treated surgically can be explained by the fact that surgical treatment is applied to the more severe and complicated cases. Only 16 (29%) patients had a favorable outcome, and these did not need fresh transplants during the course of their post-OLTx pancreatitis. Four patients (7.2%) survived the pancreatitis episode but needed to be retransplanted during or after this complication.

In summary, this study shows that several factors are involved in the development of acute pancreatitis after liver transplantation. Some of these factors are unavoidable; the prevention of others constitutes a constant goal in current practice. The study is subject to the weaknesses of a retrospective analysis. We tried to identify possible contributing or predisposing factors with the aim of organizing a prospective study in the future. Yet, we were unable to find a reasonable explanation for the higher incidence of pancreatitis in the hepaticojejunostomy group. Perhaps additional local factors contribute to the occurrence of this complication.

We found a strong correlation between the post-OLTx pancreatitis and hepatitis B as a primary disease for liver transplantation. The extensive nature of the mechanical dissection around the pancreas, the type of biliary reconstruction, and the number of liver grafts for the same patient seem to be contributing factors. The time that the patient remains on venovenous bypass and the quantity of IV calcium chloride administered intraoperatively are further possible predisposing factors. Unfortunately, we must conclude that in spite of the advances that have been made in the early diagnosis and treatment of these severe clinical conditions, their prognosis remains dismal.

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