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ORIGINAL ARTICLE

Gastrointestinal bleeding from enterically drained transplanted pancreas

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Summary

Gastrointestinal bleeding has been described as related complication of pancreas transplantation. Of 166 simultaneous pancreas kidney transplantations, 61 were enteric-drained pancreas transplants (eight done with and 53 without Roux-en-Y loop). The patients were divided into two groups according to Roux (group I, $n = 8$) or no Roux (group II, $n = 53$) technique. Seven patients experienced anastomotic hemorrhage between the jejunum and duodenal stump (11%), five cases in group I and two in group II ($P < 0.001$). No relationships between gastrointestinal bleeding duodenal stump and recipient jejunum blood flow, mean pancreatic cold ischemia time, platelet count, and prothrombin time were observed. Donor age over 40 years and abnormal activated partial thromboplastin time constituted risk factors for hemorrhage from the duodenojejunal anastomosis. There were no significant differences in pancreas graft and patient survival rates between the two groups. Anastomotic hemorrhage did not influence patient and graft survival.

Introduction

Simultaneous pancreas and kidney transplantation (SKPT) is the treatment of choice for several type 1 diabetic patients affected by end-stage renal disease [1]. The first recommendation of the position statement of the American Diabetes Association, suggests that pancreas transplantation should be considered an acceptable therapeutic alternative to insulin therapy in diabetic patients with eminent or established end-stage renal disease who have had or plan to have a kidney transplant [1]. The successful addition of a pancreas does not jeopardize patient survival [2], but improves endothelial function [3]. Unfortunately, pancreas transplant is still associated with the highest surgical complication rate of all the routinely performed solid organ transplant procedures [2]. A significant number of pancreas grafts are lost early post-transplant secondary to surgical complications [2]. As William Kelly *et al.* [4] performed the first pancreas transplantation in a human being, much advancement has been introduced in order to improve the results in terms of patient and graft survival and in terms of quality of life. This pioneering experience has been followed by various techniques such as segmental pancreas transplantation with duct occlusion by neoprene [5], whole pancreas transplantation with bladder diversion [6] and, finally whole pancreas transplantation with enteric diversion (ED) [7,8]. The approach with intraductal injection has been completely substituted by whole pancreas transplantation, because of the global pancreatic fibrosis inducted by the synthetic polymers. However, the duct injection may be still useful in the salvage of the allograft in case of specific early and late complications [9]. The main advantage of bladder diversions is that it allows for detection of pancreas graft rejection by measurement of the urinary amylase levels and it allows performing a duodenum and pancreas biopsy cystoscopically [6]. Moreover, bladder diversion is safe and simple. Nevertheless, long-term success was principally limited by a high incidence of urologic complications and of readmissions for dehydration [10], which may require takedown of the

duodenocystostomy and conversion to ED [11–13]. Enteric drainage, introduced in association with segmental graft in 1970s, is becoming increasingly popular because of the satisfactory results obtained with the cystoenteric conversion [11–14]. Pancreas duct management has evolved from being bladder drainage in more than 90% of SKPT before 1996 to being ED in 71% in 1999–2001 [14]. Before the resurgence of ED, most were done with a Roux-en-Y limb of recipient jejunum, but since 1996 most were done without a Roux-en-Y [14]. Complications can arise not only from the pancreas itself but also from the simultaneously transplanted duodenum [15–18]. A reduction of the blood flow at the duodenal graft could be associated with an increased risk of anastomotic leak and hemorrhage [19]. The purpose of this study was to evaluate the incidence, diagnosis, treatment and pathologic findings of anastomotic hemorrhage between the recipient jejunum and duodenal stump of enteric-drained pancreas transplants and their impact on patient and graft survival rates. Moreover, we evaluate the reliability of intraoperative laser-Doppler measurements in predicting the occurrence of duodenal graft hemorrhagic complications.

Patients and methods

Of 166 SKPTs performed between June 1985 and January 2003, 61 (37%) were enteric-drained pancreas transplants, eight (13%) done with and 53 (87%) without Roux-en-Y loop (55 primary EDs and six cystoenteric conversions). The patients were 41 (67%) males and 20 (33%) females, with a mean age of 38 years (±6.8, range: 24–57), mean duration of diabetes of 26 (±7) years, and mean time of dialysis 31 (±19) months. The patients were divided into two groups according to Roux (group I) or no Roux (group II) technique. There were no significant differences between the two groups when we analyzed the demographic characteristics. The standard technique of organ procurements from heart-beating cadaver donors was used. Selection criteria of the donors were based primarily on the age and pancreas anatomy of the donor. Whole organ pancreaticoduodenosplenectomy was performed by an en bloc technique. In the 30 latest cases, the mesenteric root has been stapled and reinforced with a running suture. In all cases, the duodenal segment was treated with betadine plus fungizone rinsing. The kidney was likewise prepared using standard techniques. Before transplantation, the pancreas was reconstructed on the back table and splenectomy was performed. The arterial vascularization of the whole pancreatic graft was reconstructed by interposing an arterial graft of the donor iliac branching. In 69% of cases we have also reconstructed the gastroduodenal artery using the Y graft. The proximal and the distal end of the graft duodenum are closed with a staple line followed by inversion with 3-0 Vycril sutures. The whole organ pancreas was transplanted in the right iliac fossa through an intraperitoneal approach. The donor common iliac artery was anastomosed end-to-side to the recipient right external or common iliac artery. Systemic venous drainage is obtained by anastomosing the donor graft portal vein to the recipient iliac vein. In portal venous drainage, the portal vein of the allograft is anastomosed to the superior mesenteric vein of the recipient. The duodenal segment, comprising the first, second, and third portion of the donor duodenum was anastomosed side-to-side to a Roux-en-Y loop of the recipient jejunum (eight cases) and in the remaining 53 a side-to-side duodenojejunal anastomosis was used. For the duodenojejunal anastomosis, a hand running suture in two layers with 4-0 of Vycril was performed. Recipient jejunum and duodenal graft microcirculation was evaluated intraoperatively. Blood flow recordings were obtained with a laser-Doppler flowmetry technique (Periflux, Perimed, Stockholm, Sweden). The probe had one emitting and two receiving fibers, with a diameter of 0.7 mm and separation of 0.7 mm. The instrument set up has been used in clinical studies of intestinal microcirculation [20,21]. The kidney transplant was performed in the left iliac fossa, with end-to-side vascular anastomosis between the renal vessels and left external iliac vessels. Finally, an extravesical ureteroneocystostomy by standard techniques was performed. The immunosuppressive protocol consisted of a quadruple sequential regimen of azathioprine, prednisone, antilymphocyte globulin, cyclosporin A. Since January 1998, mofetil mycofenolate replaced azathioprine and since January 1999, FK506 (tacrolimus), and cyclosporin A were alternatively used. All recipients had perioperative antibiotics that included a third generation cephalosporin 1 g three times a day, which was discontinued when fever disappeared, and fluconazole 200 mg/day for 10 days after the transplant. Prophylactic treatment of cytomegalovirus (CMV) infections was based on specific globulins in CMV-negative patients, followed by acyclovir in all patients. Postoperatively, calcium heparin (0.2 ml three times a day) was used in 20 cases while in the remaining 41 enoxaparin was used at a dosage of 2000/4000 IU according to the recipient body weight. Maintenance antiplatelet treatment consisted of aspirin 100 mg once a day. No protease inhibitors have been used. The activated partial thromboplastin time (APTT) values were evaluated at the time of the hemorrhage and correlated with the incidence of gastrointestinal bleeding. Seven of 61 patients (11%) (five of group I and two of group II) were identified with anastomotic hemorrhage between the distal jejunum and duodenal stump within 1 week after the transplant or cystoenteric conversion. The postoperative CMV antigenemia tests were

Table 1. Operative and pathologic findings, treatment, and pancreas graft outcome in seven patients with hemorrhage from the duodenojejunal anastomosis in enteric-drained pancreas transplant.

Case report	Operative findings	Intervention	Outcome of pancreas graft	Surgical specimen	Pathologic findings
1	Active anastomotic bleeding ulcer	Graft pancreatectomy	Lost for thrombosis	Pancreas and duodenum	Duodenal ulcers with severe duodenitis, short or absent villi, hemorrhage and vascular ectasia
2	Pancreas graft thrombosis	Graft pancreatectomy	Lost for thrombosis	Pancreas and duodenum	Duodenal ulcers with moderate duodenitis, short or absent villi, hyperemia and vascular ectasia
3	Recurrent active anastomotic bleeding ulcer	Three relaparotomies (two localized hemostasis and one redo of the duodenum-jejunum anastomosis)	Functioning	Ileum	Severe active ileitis with edema
4	Active anastomotic bleeding ulcer	Localized hemostasis	Functioning	Pancreas biopsy	No rejection
5	Active anastomotic bleeding ulcer	Localized hemostasis	Functioning	–	–
6	Active anastomotic bleeding ulcer	Allograft pancreaticoduodenectomy and duct occlusion of the remaining segmental graft	Functioning	–	–
7	No surgery	Medical treatment	Functioning	–	–

positive in three of seven patients within the following 2 weeks after the transplant. Five cases of group I and one of group II were operatively managed. Causes for surgery were a massive lower gastrointestinal bleeding with significant blood loss precipitating an episode of hypovolemic shock, severe hypotension, and hemodynamic instability. The treatment and pathologic findings are depicted in Table 1.

Statistical analysis

All the data were expressed as mean ± SE. Data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with Levene's test. Actuarial pancreas graft and patient survival rates were computed by Wilcoxon life-table analysis. For comparison of survival rates the log-rank test was used. Categorical variables were analyzed using the chi-square test. Two-sided paired Student's *t*-test was used to compare paired data. A *P*-value of <0.05 (by two-tailed testing) was considered an indicator of statistical significance. Analysis of data was done using the STATISTICAL PACKAGE FOR THE SOCIAL SCIENCE 11 software (SPSS, Inc., Chicago, IL, USA).

Results

The two groups were matched for age, gender, duration of diabetes, and duration of dialysis. There was a significant difference between transmural blood flow values of the duodenal stump when compared with recipient jejunum ($P < 0.01$) (Fig. 1). No relationship between blood flow variation and the occurrence of gastrointestinal bleeding was observed. Gastrointestinal bleedings from the anastomosis between the jejunum and the duodenal stump were observed in five of eight (62%) cases of

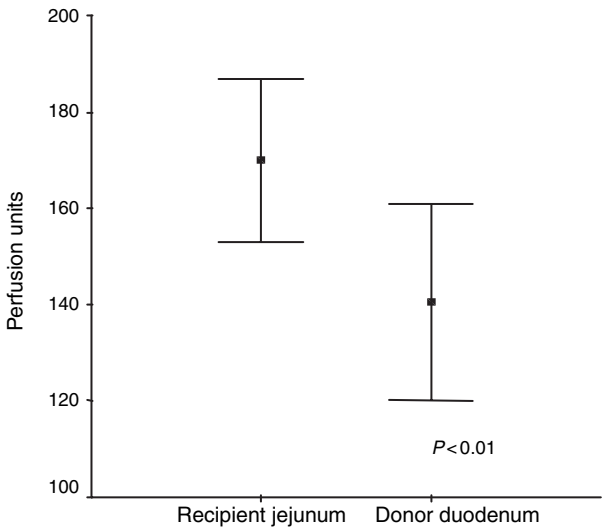

Figure 1 Intraoperative recipient jejunum and duodenal graft transmural laser-Doppler flowmetry ($n = 61$ patients). Perfusion unit (1 = 10 mV).

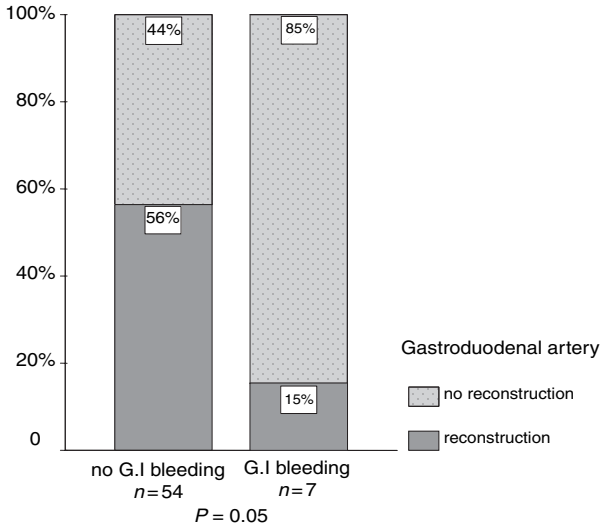

Figure 2 Effect of donor gastroduodenal artery reconstruction on gastrointestinal bleeding rates.

group I and in two of 53 (3.7%) of group II ($P < 0.01$). The mortality because of bleeding was 0%. Six of seven patients were managed operatively (Table 1). Five of seven (71%) of the pancreatic grafts are still functioning. Two grafts were lost as a result of thrombosis (one in group I and one in group II). The rate of gastrointestinal bleeding was lower in patients who received a pancreatic graft with back table reconstruction of the gastroduodenal artery ($P = 0.05$, Fig. 2). No relationships between gastrointestinal bleeding and duodenal stump and recipient jejunum blood flow, mean pancreatic cold ischemia time, types of antithrombotic prophylaxis used, platelet count, and prothrombin time were observed (Fig. 3; panel a–c). Donor age over 40 years and abnormal APTT constituted risk factors for hemorrhage from the duodenojejunal anastomosis (Fig. 3; panel d, e). Donor age 40 or older was the only risk factor for hemorrhage from the duodenojejunal anastomosis ($P = 0.01$). The pathologic study of the removed grafts showed (Fig. 4) a normal histologic pancreatic parenchyma. The duodenal segment had multiple-wide ulcers with severe-to-moderate inflammation and edema (Fig. 4, panel a, b). Immunohistochemistry stains for CMV (Dako, Glostrup, Denmark) on one or more suspicious areas from formalin-fixed, paraffin-embedded slides was always negative (Fig. 4, panel c). The median pancreas graft and patient survival time was 144 and

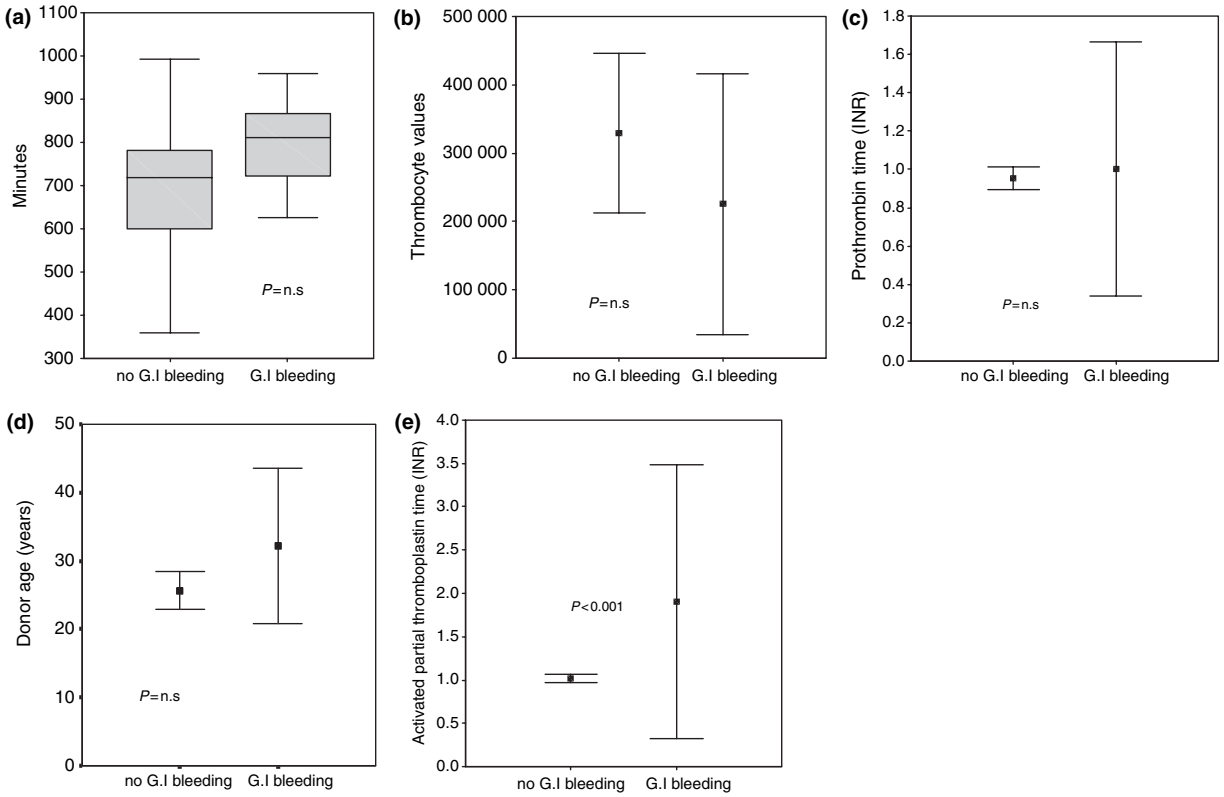

Figure 3 Relationships between mean pancreatic graft cold ischemia time (panel a), thrombocyte values (panel b), prothrombine time (panel c), donor age (panel d) and activated partial thromboplastin time (panel e) and gastrointestinal bleeding (GI).

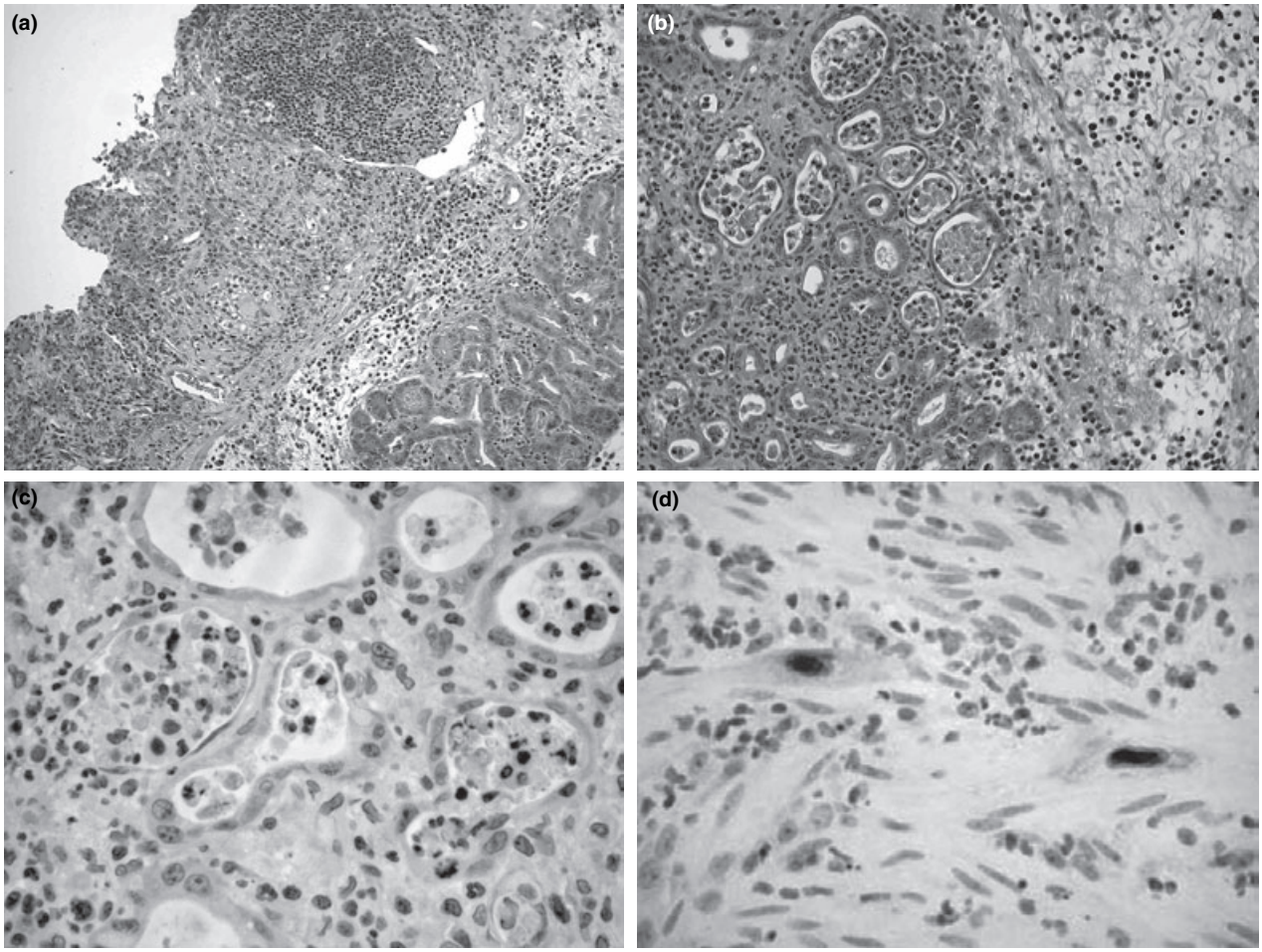

Figure 4 Histologic findings. (a) Case 1, duodenal ulcers with diffuse mucosal erosion, inflammatory infiltration, hemorrhage, and edema. Hematoxylin and eosin 125× original magnification. (b) Case 3, severe active ileitis with plasma cells and neutrophilic infiltrate. Haematoxylin and eosin 200× original magnification. (c) Case 3, like in all other cases, negative immunostaining for cytomegalovirus (CMV) both in glandular epithelial and endothelial cells. Immunostain for CMV, 200×. (d) CMV nuclear-positive immunostain (positive control case). Immunostain for CMV, 200×.

72 months for cases with or without gastrointestinal bleeding. There was no significant difference between the overall pancreas and patients survival curves (Fig. 5, panel a, b) in patients with or without gastrointestinal bleedings.

Discussion

Since the first SKPT performed by Kelly *et al.* in 1967 [4], several techniques of pancreas transplantation have been proposed. The procedure has evolved over the last 20 years, and refinements in technique, better organ preservation solutions, and more effective immunosuppressive therapies have improved 1-year graft survival rates to 95% in the last era [14]. From 1987 to 1995, most transplants were performed with systemic bladder drainage by the duodenal segment technique. Bladder drainage has contributed to achieve better results in terms of patients and grafts survival. Unfortunately, the adoption of this technique has resulted in a wide spectrum of intractable urologic complications, which could require cystoenteric conversion. Because of a favorable experience with enteric conversion a resurgence of interest occurred in primary enteric drainage in order to avoid the complications of bladder drainage [11–13]. Since 1995, the number of pancreas transplants performed with primary enteric drainage has steadily increased, accounting for 71% of cases in 2001 [14]. This procedure is most physiologic of all duct management techniques, but increased risks of abdominal complications related to small bowel surgery are reported. ED may be done with or without the use of a Roux-en-Y loop, but there has been an increased tendency to avoid Roux-en-Y technique, as reported in International Pancreas Transplant Registry [14]. Complications can

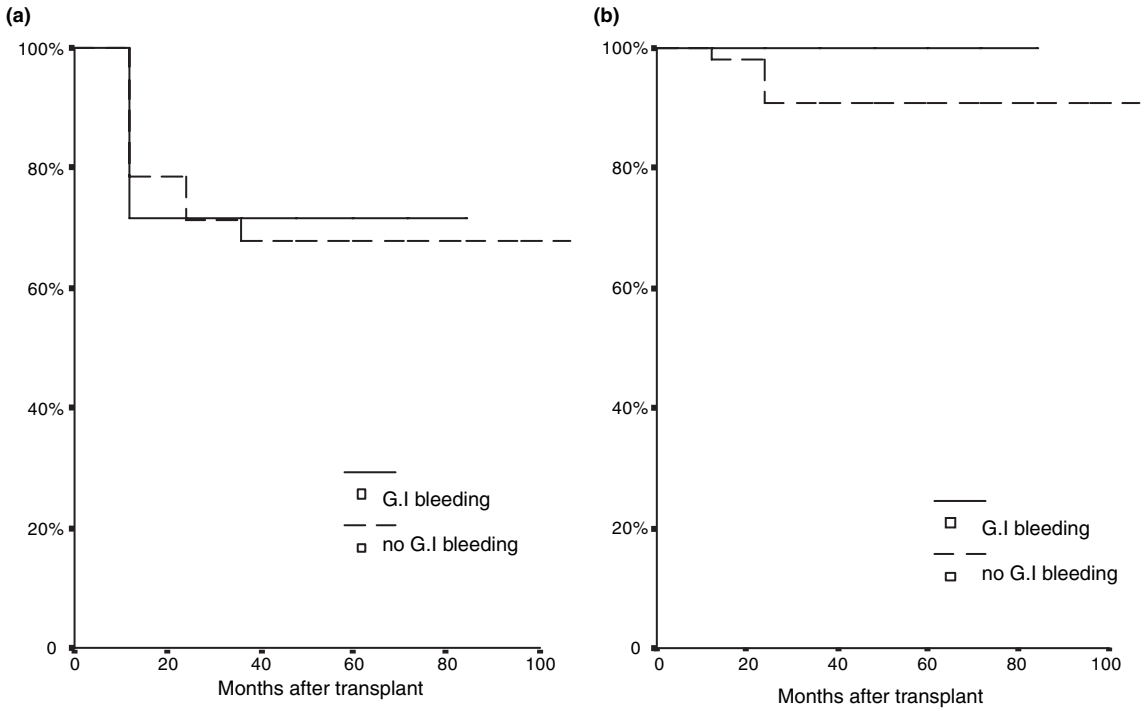

Figure 5 Actuarial pancreas graft (panel a) and patient survival (panel b) in cases with and without gastrointestinal bleeding (GI). No significant difference was noted.

arise not only from the pancreas itself but also from the simultaneously transplanted duodenum. The incidence of gastrointestinal bleeding early and late after an ED pancreas transplant is unknown [15]. Stratta *et al.* described three cases of hematuria because of duodenal segment bleeding caused by invasive CMV duodenitis in bladder drained SKPT [16]. Moreover, ulcerations with bleeding have been reported in the duodenal cuff of the transplanted pancreas and are very often secondary to CMV infection [13]. Barone *et al.* [15] reported a case of late-gastrointestinal bleeding as a result of an ulcer in the transplant duodenum secondary to CMV infection. Gastrointestinal bleedings from the duodenojejunal anastomosis probably could be minimized by careful preparation and handling of the duodenum segment to avoid devascularization. The seven cases presented in this report are examples of hemorrhagic complications following enteric-drained SKPT. In our experience, the gastrointestinal bleeding occurred early and, in the cases surgically treated, an ulcer of the anastomosis between the duodenal stump and the recipient jejunum was the most common site of hemorrhage. In two cases, the hemorrhage was secondary to the venous thrombosis. The most common clinical symptom was abdominal pain ($n = 7$), followed by a massive lower gastrointestinal bleeding with severe hypotension ($n = 6$). Findings during clinical examination indicated the need for intervention in six cases. Six of the seven cases observed required operative intervention such as open surgical localized hemostasis ($n = 2$), a redo of the duodenojejunal anastomosis ($n = 1$), pancreaticoduodenectomy with duct occlusion of the remaining segmental pancreatic graft ($n = 1$), and graft pancreatectomy ($n = 2$). Use of ganciclovir prophylaxis prevented CMV infection as cause of anastomotic ulcers that never showed a positive immunostain. An evident etiology for ulcers was not found but hemorrhage and edema could be related to an alterated microperfusion at the duodenal graft demonstrated by a decreased blood flow recorded with intraoperative laser-Doppler flowmetry. We found significant difference in the gastrointestinal hemorrhagic complication rates between recipients who underwent the Roux-en-Y duodenoenterostomy and those with a side-to-side duodenojejunum anastomosis. No one death related to the hemorrhage itself was recorded. The hemorrhage from the duodenojejunal anastomosis in enteric-drained pancreas transplant had only a small impact on outcome. Two grafts were lost; the remaining five have a good graft function after a mean follow up of 44 months. Patients and pancreatic allograft survival rates were similar in patients with or without gastrointestinal bleeding. Based on this single center retrospective experience, we believe

that enteric-drained SKPT is associated with a finite risk of gastrointestinal bleedings (11% of our cases) that are an important source of morbidity but with early diagnosis and prompt treatment (open surgery or, rarely only medical treatment) can result in high rate of graft salvage. Laser-Doppler flowmetry could be a future useful technique in order to evaluate the duodenal microperfusion.

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