Pancreas Transplants Venous Graft Thrombosis: Endovascular Thrombolysis for Graft Rescue

Marta Barrufet · Marta Burrel · M. Angeles García-Criado ·
Xavier Montaña · M. I. Real · Joana Ferrer · Laureano Fernández-Cruz ·
Rosa Gilabert

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Abstract

Purpose To retrospectively assess the efficacy and safety of percutaneous endovascular treatment in patients with pancreas venous graft thrombosis (PVG).

Materials and Methods Between 2001 and 2009, 206 pancreas transplants were performed at our institution. A retrospective review of pancreas graft recipients who underwent endovascular therapy for PVGT was performed. The study group included 17 patients (10 men, 7 women; mean age 38 years) with PVGT (<60 % [9 patients]; 30–60 % [8 patients]) 6.6 ± 5.7 days after grafting. The angiographic studies, type of endovascular procedure, endovascular procedural and postprocedural effectiveness, and patient and graft outcomes were assessed.

Results In 16 of 17 cases (94 %), significant (87.5 %) or partial (12.5 %) lysis of thrombi was achieved. One patient had external compression of the portal vein due to a hematoma, which hindered mechanical removal of the

thrombi. This patient required graft pancreatectomy for extensive areas of parenchymal necrosis 2 days after the endovascular procedure. No complications related to endovascular treatment were observed. Postprocedural bleeding episodes related to anticoagulation were observed in five patients. Patient and pancreas graft survival rates at 12 months were 94 and 76 %, respectively.

Conclusion Catheter-directed thrombectomy is an effective treatment for patients with PVGT. Percutaneous thrombectomy, followed by anticoagulation, appears to be an effective therapy to remove the thrombus and is associated with a low complication rate.

Keywords Pancreas transplantation · Venous graft thrombosis · Percutaneous thrombectomy

Introduction

Technical failure is responsible for more than half of all pancreas graft lost in the first 6 months after transplantation [1, 2]. Vascular thrombosis accounts for the majority

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M. Barrufet (✉) · M. Burrel · M. Angeles García-Criado ·
X. Montaña · M. I. Real · R. Gilabert
Diagnostic Imaging Center, Hospital Clinic University of
Barcelona, Villarroel 170, 08036 Barcelona, Spain
e-mail: barrufet@clinic.ub.es

M. Burrel
e-mail: BURREL@clinic.ub.es

M. Angeles García-Criado
e-mail: MAGARCIA@clinic.ub.es

X. Montaña
e-mail: JMONTANA@clinic.ub.es

M. I. Real
e-mail: mirealmarti@clinic.ub.es

R. Gilabert
e-mail: GILABERT@clinic.ub.es

J. Ferrer
Liver Surgery and Transplantation Unit, Hospital Clinic
University of Barcelona, 08036 Barcelona, Spain
e-mail: JOFERRER@clinic.ub.es

L. Fernández-Cruz
Surgery Department, Hospital Clinic University of Barcelona,
08036 Barcelona, Spain
e-mail: LFCRUZ@clinic.ub.es

of these early graft losses with an approximate 2:1 ratio between venous and arterial graft thrombosis [3]. Contributing factors to PVGT include the following: diabetes, organ preservation and procurement, and grafting technical aspects [1–3]. Particularly relevant is the effect caused by grafting an organ with relatively low blood flow due to the loss of splenic circulation, which reduces flow in the splenic artery (SA) and vein (SV) where thrombosis commonly develops. To prevent graft thrombosis, most centers use perioperative graft thrombosis prophylaxis protocols, although the effectiveness of such has yet to be proven in a prospective randomized study [2].

Imaging techniques have an important role in the diagnosis of pancreas graft technical failure complications. Color Doppler ultrasonography (CDUS), currently the first-line technique in postoperative pancreas graft monitoring, enables early diagnosis of PVGT, thus increasing the possibility of graft-rescue treatments. Graft-rescue treatments include anticoagulation, surgical thrombectomy, and endovascular treatment [4–11].

The aim of this study was to retrospectively assess the efficacy and safety of percutaneous endovascular treatment in patients with PVGT.

Materials and Methods

This retrospective observational study received Institutional Review Board approval. Between January 2001 and December 2009, 206 pancreas transplantations (181 simultaneous pancreas–kidney transplants (SPK) were performed in our institution. In 29 patients with CDUS diagnosis of venous graft thrombosis angiographic examination was performed.

All patients were enteric-drained and had systemic venous outflow. The surgical procedure has been previously reported [8]. The superior mesenteric artery (SMA) was distally dissected and sewn to the SA in an end-to-end fashion. In most cases, the proximal SMA with an aortic patch was anastomosed to the recipient common iliac artery (Supplemental material Figure 1). In a few cases, the arteries were reconstructed with an iliac arterial “Y” graft (Supplemental material Figure 2). The venous anastomoses were performed between the portal vein (PV) of the graft and the vena cava or the common iliac vein of the recipient to create an end-to-side anastomosis. The pancreas was preserved under cold-storage conditions with University of Wisconsin solution, with a mean cold ischemia time of 11.4 ± 4.1 h (range 5–21), in the majority of cases.

Anticoagulation prophylaxis was started with low molecular-weight heparin (LMWH) (2,500 UI dalteparin/12 h) and acetylsalicylic acid 50 p.o. On postoperative day 10, LMWH was discontinued and acetylsalicylic acid

increased to 100 mg p.o. on a daily basis indefinitely. Patients received quadruple induction immunosuppressive therapy: tacrolimus, mycophenolate mofetil, prednisone, and basiliximab for SPK or antithymocyte globulin for pancreas retransplantation, pancreas after kidney (PAK) transplants, or pancreas transplantation alone (PTA).

CDUS was used for graft surveillance at 24 and 72 h after grafting and weekly thereafter until discharge or when clinically indicated. Pulsed doppler and colour doppler examinations included assessment of arterial and venous graft vessels from the iliac anastomosis, which were carefully followed along the graft until the distal portion of the mesenteric and SA and SV (Fig. 1). In addition, the arterial and venous spectrums were obtained at parenchyma level (head, body, and tail). The arterial waveform was quantified by the resistive index ($=\text{peak systolic velocity} - \text{end-diastolic velocity} / \text{peak systolic velocity}$). Doppler parameters were adjusted to optimise the detection of low blood flow velocities [8]. Since 2002, ultrasound equipment with contrast-enhanced ultrasound study (CEUS) capability has been available. When CDUS was suboptimal due to an exploration angle $<60^\circ$, or when a confident diagnosis could not be achieved because an anechoic vein with no flow was observed, CEUS was performed after injection of 2.4 ml of sulphur hexafluoride (SonoVue; Bracco, Milan, Italy) followed by a flush of 5 ml bolus of saline using a low mechanical index (MI 0.21). The CDUS diagnosis of PVGT was made when echogenic or hyperechogenic material filling the vein was observed. On CEUS studies, the thrombus appeared as a hypoechoic non-contrast-enhanced filling defect in the vein.

Patients

In 29 of 206 patients, CDUS study identified thrombus filling $>60\%$ of the splenic and/or mesenteric pancreas graft veins with maintenance of venous flow peripheral to the thrombus. A low-resistance arterial doppler waveform ($RI < 0.75$) was also obtained at the hilar and parenchyma levels in all patients. In 6 of these patients, CEUS was also performed. There were 19 men and 10 women with a mean age of 38.8 years (range 23–54). Of these 29 pancreatic grafts, 21 were SPK, 2 were PAK, 2 were PTA, and 4 patients had undergone pancreas retransplantation.

In all 29 patients, angiography was performed with the aim to proceed with a therapeutic procedure. The CDUS and angiographic studies were nonconcordant with regard to thrombi extension in 10 patients. In 7 of these 10 patients, the splenic and/or mesenteric pancreas graft thrombosis extension was $<30\%$ on direct venography, and hence no endovascular treatment was performed. In 2 other patients, arteriography confirmed the venous thrombosis but also disclosed a complete arterial thrombosis in one patient and a severe stenosis at the arterial anastomosis

Fig. 1 CDUS in the postoperative evaluation of the transplanted pancreas. **(A)** Color Doppler of the venous anastomosis discloses a continuous flow with minimal pulsatility. **(B)** Color Doppler of the arterial anastomosis discloses a low-resistance Doppler waveform:

peak systolic velocity with continuous flow during diastole. **(C)** Color Doppler with correct patency of the PV and the SMV. **(D)** Color Doppler with correct patency of the SA and the SV

in another; both patients underwent surgery. In the remainder of the patients, isolated partial arterial thrombosis was depicted and successfully treated with chemical thrombolysis.

In 19 of 29 patients, angiography disclosed a thrombosis extension >60 % of either the SV or the SMV in 11 (CEUS performed in 6 patients) and from 30 to 60 % in 8 patients (no CEUS performed). In 2 patients with complete vein thrombosis, angiography showed collateral venous vessels, and thus no treatment was required. The remaining 17 patients were candidates for endovascular treatment and are the subjects included in the analysis. No intrapancreatic venous thrombosis was detected on pretreatment selective angiography, including arterial, parenchymal, and venous phases, or on selective venography in these patients.

Angiographic Procedure

Angiographic studies were performed by two interventional radiologists with >20 years of experience and reviewed by two interventional radiologists with >5 years of experience. The mean time from CDUS diagnosis to treatment with catheter-directed thrombectomy and/or chemical thrombolysis was

11.3 ± 14 h (range 1–57). Mechanical thrombectomy alone was used in 15 cases. One patient was treated with mechanical thrombectomy and thrombolysis. The remaining patient was treated with chemical thrombolysis alone.

First angiography of the internal iliac artery was performed to locate the surgical graft anastomosis. A 5F hydrophilic Cobra catheter (Radiofocus; Terumo Europe) was used to catheterize the donor mesenteric-SA, and selective angiography, including arterial, parenchymal, and venous phases, was performed (Fig. 2). Once the thrombus was confirmed, selective catheterization of the SV and/or the mesenteric vein and direct venography was performed through the femoral vein.

Percutaneous mechanical thrombectomy was performed using an Angiojet catheter (6F hydrodynamic device). When chemical thrombolytic therapy was applied, urokinase was infused. Lysis of the thrombus and restoration of flow in the SV or the SMV was documented on immediate follow-up direct venography (Fig. 3).

To evaluate postprocedural effectiveness, venous permeability and degree of lysis were divided into four categories: (1) no thrombosis, (2) significant lysis with minimal thrombi filling one-third or less of the vein, (3) partial lysis

Fig. 2 Angiographic procedure. Normal findings. (A) Aortiliac angiography to localize the surgical graft anastomosis. (B) Selective angiography of the donor SMA with a patent SMA and SA.

(C) Indirect venography with partial thrombi in the SV and a patent SMV. (D) Direct venography with partial thrombi (*asterisk*) in the SV

with thrombi filling between one to two-thirds of the vein, and (4) persistence of significant thrombus filling more than two-thirds of the vein.

Follow-Up

The patients were monitored closely with the CDUS follow-up protocol. Once CDUS showed resolution or stabilization of the residual clot, patients were switched to oral anticoagulation or to LMWH combined with antiplatelet therapy for 3–6 months. Afterward, they were kept on antiplatelet therapy. Patient and pancreas graft survival as well as complications, including rethrombosis and bleeding episodes, were assessed.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 software. Results were expressed as mean (range). Survival time (Kaplan–Meier analysis) was evaluated from the day of initial treatment to the day of the end of follow-up or graft failure regardless of the cause of graft failure.

Results

PVGT, determined by the time of sonographic diagnosis, occurred at a mean postoperative time of 6.6 ± 5.7 days (range 1–22; Table 1). Four patients with PVGT <60 %

Fig. 3 Follow-up of a complete SV vein thrombosis by different imaging techniques (Table 1; Patient 3): **1A** Color Doppler (CDUS) demonstrating a complete thrombus (arrows) at POD four. **1B** Contrast-enhanced ultrasound (CEUS) demonstrating a complete thrombus (arrows) at POD four. **1C** Direct venography (DSV) demonstrating a complete thrombus (arrows) at POD four. **2A** CDUS at 2 days follow up after mechanical thrombectomy shows residual clot (asterisk) of the SV at its proximal portion. **2B** CEUS 2 days

follow up after mechanical thrombectomy shows residual clot (asterisk) of the SV at its proximal portion. **2C** DSV (c) at 2 days follow up after mechanical thrombectomy confirms residual clot (asterisk). **3A** DSV after the second MT shows minimal residual thrombi within the vein. **3B** Follow-up CDUS after the second MT shows minimal residual thrombi within the vein. **3C** Follow-up CEUS after the second MT confirms the presence of a minimal residual thrombi within the vein

and 1 patient with <60 % thrombosis had abnormal laboratory tests hyperglycemia (>110 mg/dl; 1 patient), hyperamylasemia (>104 U/l; 5 patients), and increased lipase levels (<145 U/l; 5 patients).

Analysis of Angiographic Postprocedural Effectiveness

Significant lysis of the thrombi was seen 13 patients. Partial lysis was observed in 3 patients (nos. 3, 6, and 9) (Table 1). These three patients required further treatment after the endovascular procedure: 1 patient (no. 3) developed graft rethrombosis 2 days after the procedure, and a new mechanical thrombectomy was performed with minimal

residual thrombi within the vein after this second procedure. Another patient (no. 6) had severe stenosis of the venous anastomosis observed on venography and was treated with surgical intervention 9 days after the endovascular treatment; a fibrous reaction with entrapment of the PV and the right ureter was observed and was managed with sectioning of the adhesions. Doppler follow-up studies showed a progressive decrease in the size of the SV thrombi. The third patient (no. 9) had external compression of the PV, which hindered mechanical removal of the thrombi. Computed tomography (CT) performed on follow-up showed an enlarged, ill-defined pancreatic graft with subtle and heterogeneous contrast enhancement. PV

Table 1 Transplant outcome for patients with venous or arterial thrombosis

Patient	Age/ sex	Transplant type	Thrombosis	Days from surgery to diagnosis	Hours from diagnosis to thrombolysis	Endovascular technique	Result	Technical success	Graft loss POD	Cause of graft loss	Graft survival
1	42/ M	SPK	TSV 60–100 %	3.45	2.35	MT	No residual thrombi	Yes			67.54 months
2	40/ M	SPK	TSV 60–100 %	1.68	21.23	MT	TSV 0–30 %	Yes			90.54 months
3a	48/ M	PAK	TSV 60–100 % ^a	4.52	5.18	MT	TSV 30–60 %	Yes			
3b	48/ M	PAK	TSV 60–100 % ^a	6	7	MT	TSV 0–30 %	Yes	7.5 months	Rejection	7.5 months
4	52/ M	PAK	TSV 60–100 % ^a	8.5	1.85	MT	TSV 0–30 %	Yes			54.36 months
5	40/ M	SPK	TSV 60–100 % ^a	6.57	21.23	MT	TSV 0–30 %	Yes	15 days	Enteric leak	15 days
6	47/F	SPK	TSV 60–100 % ^a	7.58	3.87	MT	TSV 30–60 %	Yes	11 months	Rejection	11 months
7	29/F	Retransplant	AT with distal recanalization TSV 60–100 %, TSMV 60–100 % ^a	1.57	11	MT + thrombolysis	TSV 30–60 %, TSMV 0–30 %	Yes			83.9 months
8	28/F	SPK	TSMV 60–100 %	5	57	Thrombolysis	TSMV 0–30 %	Yes			126.23 months
9	23/F	SPK	TSV 30–60 %, TSMV 60–100 % ^a	2.56	6.7	MT	TSV 0–30 %, TSMV 30–60 %	Yes	4 days	Venous thrombosis; graft compression by surrounding hematoma	4 days
10	32/ M	Retransplant	TSV 30–60 %	2.55	0.83	MT	TSV 0–30 %	Yes			96.66 months
11	43/ M	SPK	TSV 30–60 %	NV	NV	MT	TSV 0–30 %	Yes	14.2 months	Rejection	14.2 months
12	45/ M	SPK	TSV 30–60 %	10.54	4.67	MT	TSV 0–30 %	Yes	40.6 months	Rejection	40.6 months
13	42/ M	SPK	TSV 0–30 %, TSMV 30–60 %	5.44	6.52	MT	No residual thrombi, TSMV 0–30 %	Yes			39.7 months
14	31/F	SPK	TSV 30–60 %	9.4	4	MT	TSV 0–30 %	Yes			45.21 months
15	29/ M	SPK	TSMV 30–60 %	7.53	5	MT	TSMV 0–30 %	Yes			85.9 months

Table 1 continued

Patient	Age/ sex	Transplant type	Thrombosis	Days from surgery to diagnosis	Hours from diagnosis to thrombolysis	Endovascular technique	Result	Technical success	Graft loss POD	Cause of graft loss	Graft survival
16	42/F	SPK	TSV 30–60 %	2	15.6	MT	TSV 30–60 %	No lysis			94.95 months
17	36/F	SPK	TSMV 30–60 %	12		MT	TSV 0–30 %	Yes			10.5 years

TSV thrombosis of the SV, TSMV thrombosis of the SMV, AT arterial thrombosis, MT mechanical thrombolysis, POD postoperative day, 3b rethrombosis 12 h after initial treatment, NV not available

^a CEUS

anastomosis with the IVC graft was compressed by a 4-cm hematoma, and the proximal portion of the SV and the mesenteric vein were thrombosed. This patient required graft pancreatectomy for extensive areas of parenchymal necrosis 2 days after the endovascular procedure. In one patient (no. 16) with partial thrombus (30–60 %), mechanical thrombectomy was unsuccessful.

Complications

No complications related to the endovascular treatment were observed. Five patients presented postprocedural bleeding complications (range 6 to 10 days) related to anticoagulation: hematuria ($n = 2$), melena ($n = 2$), and pelvic hematoma ($n = 1$) (Table 2). Four patients had hemodynamic instability with decreased hematocrit (range 7–9 points), which required blood transfusion. In the remaining patient, bleeding control was obtained by replacing endovenous heparin with LMWH. One patient (no. 5), 15 days after pancreas transplantation and 1 week after mechanical thrombectomy, developed pancreatocenteric fistula leading to graft pancreatectomy. The patient died 8 months later from septic peritonitis.

Patient and Graft Survival

Mean follow-up in endovascular-treated patients was 69.4 months (range 4 days to 10.5 years). Sixteen patients were alive at the time of their most recent available clinical and radiological reports.

Patient survival was 94 %. Pancreas graft survival rates at 6 months, at 1 year, and at 5 to 10 years were 88, 76, and 65 %, respectively (Fig. 4). Four patients had chronic rejection diagnosed at 7.5, 11, 14, and 40.6 months after surgery, respectively. In one patient (no. 16), despite unsuccessful treatment with mechanical thrombectomy, remained normoglycemic with an HbA1c value of 5.6 % at 56 months after thrombectomy. No venous or arterial thrombosis was diagnosed in patients with a functioning pancreas graft on long-term follow-up (see Table 1).

Discussion

Total SV and SMV thrombosis poses significant risks to the transplanted pancreas resulting in acute ischemia and allograft necrosis and thus leading to graft transplantectomy.

The management of PVGT is controversial. Although there are no consensus guidelines about the best therapeutic option, it is clear that for graft salvage, treatment must be performed promptly. Treatment choice depends on thrombosis location and extension, operator experience, and availability of skilled interventional radiologists [3].

Table 2 Postprocedural complications

Patient no.	Postprocedural bleeding complications	Time from thrombectomy (d)	Hemodynamic instability	Hematocrit decrease
2	Hematuria	6	Yes	9
4	Hypogastric hematoma	2	Yes	7
11	Melenas	4	Yes	8
13	Hematuria	10	Yes	8
17	Melenas	3	No	1

Fig. 4 Failure-free survival of pancreas graft after transplant

Kuo et al. [6] and Ciancio et al. [7] reported that venous thrombosis after pancreas transplantation could be treated with heparin and subsequent oral anticoagulation or aspirin depending on the thrombus extension. However, in the study of Kuo et al. [6], the results of anticoagulation treatment were significantly worse in the recipients of solitary pancreas transplantation (26.8 %) compared with the recipients of simultaneous kidney and pancreas transplantation (86.1 %) despite the fact that venous graft thrombosis was diagnosed earlier in patients with solitary pancreas transplantation.

The reported experience with surgical thrombectomy has been limited to a series of few patients with total vein thrombosis [4, 11]. Recently Fridell et al. [5] reported 343 pancreas transplants, in which early urgent re-exploration for suspected graft pancreas thrombosis was indicated based on the presence of an unexplained hyperglycemia or the failure to achieve euglycemia 1 week after grafting. This approach resulted in 35 early surgical re-explorations with the graft being compromised in 20 (57 %) cases, 10 of which involved venous thrombosis. Surgical thrombectomy was performed in six grafts with graft rescue in five cases.

Since the late 1990s, successful interventional radiologic procedures, including chemical thrombolysis and mechanical thrombectomy, have been reported in small series of patients with PVGT [8–10]. Mechanical thrombectomy

offers the direct targeting of SV and mesenteric vein thromboses through the femoral vein in patients with systemic venous drainage, thus allowing removal of the thrombus and restoration of outflow. In the study of Stokland et al. [12], the largest series reported to date, a group of 6 symptomatic patients with total pancreas vein thrombosis treated with endovascular pharmacomechanical techniques achieved 50 % graft survival with 100 % patient survival (mean follow-up 373 days).

Pharmacomechanical angiographic techniques are routinely used in our institution, and the excellent initial results obtained in PVGT support the angiographic interventional approach [8]. Our study evaluated the long-term results of pharmacomechanical angiographic techniques in a group of 17 patients with PVGT. In 14 of 17 pancreas grafts (82 %), significant lysis of the thrombi was obtained. No direct procedure-related complications were observed in our group analysis, but complications associated with anticoagulation were noted in 5 patients. Only in 2 grafts was further treatment was required: 1 new thrombolytic procedure and 1 surgical reconstruction of the stenotic venous anastomosis.

Although the assessment of the ultrasound contrast agents was not the aim of this analysis, their use is particularly appealing for noninvasive delimitation of the extension of the thrombus and thus for patient selection for interventional procedures. CEUS was concordant with angiography in all patients in whom it was administered. In contrast, 41 % of the patients with PVGT diagnosed as suitable candidates for a pharmacomechanical angiographic procedure by CDUS were considered inappropriate by preprocedural angiographic study. This probably reflects the fact that in slow-flow situations in which the vein lumen is not anechoic but filled with a low level of echoes, CDUS overstates the length of the thrombi or cannot differentiate echoes due to slow flow due to vein thrombosis. Thus, a contrast imaging technique is advisable to stage thrombus length in the SV and mesenteric vein. It must be taken into account that intrapancreatic vein indemnity is only indirectly assessed on CDUS by the presence of low arterial resistance at the pancreas graft parenchyma. CEUS is a real-time study that allows patency evaluation of large veins as well as graft parenchyma

perfusion with depiction of the intrapancreatic arteries and veins. CT angiography (CTA) can provide a precise map of the intrapancreatic veins [13], but the advantage of CE US over CTA is the avoidance of ionizing radiation and contrast-agent injection, with the latter being particularly important during the early postoperative period to avoid worsening renal function.

The retrospective design is the limitation of this study. The lack of randomization and a control group treated with anticoagulation prevents to assess in what number of these patients, particularly those with thrombus 30–60 % in length, anticoagulation alone would have been effective. The current literature dealing with the available salvage strategies is retrospective without comparing the different treatment options [4–12]. The low incidence of PVGT makes it difficult to compare the treatment options in a prospective randomized study in a single institution.

Although in recent years the identification and correction of predisposing factors of PVGT has reduced its incidence, it still adversely affects graft outcome. CDUS is the primary imaging technique for monitoring vascular patency. Its limitation lies in the suboptimal definition of thrombus extension. We believe that contrast imaging should be performed for selection of the appropriate treatment. Percutaneous thrombectomy followed by anticoagulation appears to be a safe and effective therapy to remove pancreas venous graft thrombi.

Conflict of interest Marta Barrufet, Marta Burrel, M. Àngeles García-Criado, Xavier Montaña, MI. Real, Joana Ferrer, Laureano Fernández-Cruz, Rosa Gilabert authors have no conflict of interest.

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