Immediate post-operative complications (I): Post-operative bleeding; vascular origin: Thrombosis pancreatitis

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Abstract

Simultaneous pancreas-kidney transplantation is the treatment of choice for insulin-dependent diabetes that associates end-stage diabetic nephropathy, since it achieves not only a clear improvement in the quality of life, but also provides a long-term survival advantage over isolated kidney transplant. However, pancreas transplantation still has the highest rate of surgical complications among organ transplants. More than 70% of early graft losses are attributed to technical failures, that is, to a non-immunological cause. The so-called technical failures include graft thrombosis, bleeding, infection, pancreatitis, anastomotic leak and pancreatic fistula. Pancreatic graft thrombosis leads these technical complications as the most frequent cause of early graft loss. Currently most recipients receive postoperative anticoagulation with the aim of reducing the rate of thrombosis. Hemoperitoneum in the early postoperative period is a frequent cause of relaparotomy, but it is not usually associated with graft loss. The incidence of hemoperitoneum in the early postoperative period is a frequent cause of relaparotomy, but it is not usually associated with graft loss. The incidence of hemoperitoneum is clearly related to the use of anticoagulation in the postoperative period. Post-transplant pancreatitis is another cause of early postoperative complications, less frequent than the previous. In this review, we analyze the most common surgical complications that determine pancreatic graft losses.

Key Words: Pancreas transplantation; Vascular graft thrombosis; Postoperative hemorrhage; Graft pancreatitis; Reperfusion injury; Tissue donors; Risk factors

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Core Tip: Pancreas transplantation still has the highest rate of surgical complications among all solid organ transplants. Pancreatic graft thrombosis leads these technical complications as the leading cause of early pancreatic graft loss. Hemoperitoneum in the early postoperative period frequently requires a relaparotomy, but usually it is not
Pancreatic allograft thrombosis

Vascular thrombosis, including venous and arterial thrombosis, is one of the most severe complications following pancreas transplantation, since it continues to contribute significantly to early graft failure and loss. Thrombosis can be partial or total. Venous thrombosis has a higher incidence than arterial thrombosis (3:1)\(^2\). The incidence of complete allograft thrombosis provided in the literature ranges from 3% to 10%\(^3\)-\(^5\) while partial thrombosis incidence can be as high as 25%-30%\(^6\).

Early thrombosis occurs within the first 6 wk after the transplant, although it is more common in the first week and generally within the first 48 h after the surgery\(^7\).

Early complete venous graft thrombosis manifests as hyperglycaemia, abdominal pain over the area where the graft is located, plus melena when the drainage is enteric or haematuria and decrease in urinary-amylose production when the drainage is to the bladder. Arterial thrombosis does not express bleeding data. The suspected diagnosis is confirmed with doppler ultrasound\(^8\) and the extension of the thrombosis is assessed by computed tomography (CT) angiography, providing the necessary information to plan the best individualized treatment for each patient. Reintervention and pancreatectomy may be the best option on many occasions and explains the importance of this complication among early graft losses. The reasons why there is a greater tendency to thrombosis in pancreas transplantation, compared to other solid organ transplants, are diverse and probably multifactorial. Predisposing factors are still not well understood but include the hypercoagulable state of patients with diabetic renal failure, preservation-related graft endothelial injury and low velocity venous flow. Regarding to the pathophysiology, diabetes itself triggers a state of hypercoagulability. The decrease of the blood supply to the great vessels that allow the irradiation and venous drainage of the transplanted pancreatic graft is also proposed as a remarkable prothrombotic factor. In fact, the flow in the portal vein usually is 25% of cardiac output, around 1 L/min. The flow in the transplanted pancreas is approximately 150 mL/min, and it can be even lower if some degree of post-transplant pancreatitis occurs\(^8\). This striking decrease in the flow of the splenic vein, mesenteric superior vein and portal vein results in a clear prothrombotic situation.

Endothelial damage related to ischemia-reperfusion phenomenon and post-transplantation pancreatitis also play an important role, as demonstrated by the linear association between cold ischemia time and thrombosis rate\(^8\).

Donor risk factors associated with graft thrombosis are, as expected, similar to those described in the University of Minnesota study\(^2\) about early graft loss: (1) Donor obesity, expressed as a body mass index (BMI) higher than 30 kg/m\(^2\); (2) Donor age > 50 years old; (3) Cerebrovascular cause of death, highly correlated with age; (4) Donor Creatinine > 2.5 mg/dL; (5) Donors after circulatory death (Maastricht 2 and 3). Preliminary reports of donors with cardiac death show a substantially higher associated with graft loss. Severe pancreatitis is a major complication because it is associated with infection and can lead to graft loss.
thrombosis rate compared to donors after brain death; and (6) Total ischemia time > 20 h. There are studies that lower this ischemia time limit to > 12 h when preservation fluids other than Wisconsin are used, such as Custodiol.

Therefore, it is not surprising that the scoring systems available that attempt to assess the suitability of a pancreas donor, such as the precondition pancreas score and the donor risk index pancreas (PDRI), demonstrate greater incidence of thrombosis and graft loss in older donors with a higher BMI. The PDRI developed by Axelrod et al[8] measures the risk of organs based on 10 donor factors, such as age, BMI and cause of death, and only 1 recipient factor, the cold ischemia time. Higher PDRI correlates with higher rates of technical failure and significantly lower 1-year graft survival rates, particularly in the pancreas after kidney transplant and in isolated pancreas transplantation. The PDRI was developed after the statistical analysis of the pancreatic transplant data from the United Network for Organ Sharing Registry in the United States and has been validated in the United Kingdom for simultaneous pancreas-kidney transplantation.

The recipient-related thrombosis risk factors are less clear. Advanced arteriosclerotic disease in the recipient is usually an exclusion criterion for pancreas transplantation due to an increased risk of arterial thrombosis. However, recipient’s obesity increases the overall risk of surgical complications, such as enteric leakage, hernia or infections, but it does not increase the thrombosis rate[9]. Hereditary thrombophilic disorders can be added to recipient’s risk factors, including deficiencies of natural anticoagulants such as antithrombin, protein C and protein S, and genetic mutations such as factor V Leiden and prothrombin mutations that also contribute to an increase in risk of thrombosis. These inherited thrombophilic disorders specifically increase the risk of venous thrombosis and have a cumulative effect with other risk factors[10]. To sum up, the greater tendency to thrombosis in pancreas transplantation is not due to a single cause but rather it is a multifactorial process that includes characteristics of the donor, extraction technique, type of preservation fluid, characteristics of the recipients, surgical technique during the implant and anticoagulant therapy used (Table 1).

Clinical management

Therapeutic interventions aimed to reduce thrombotic graft loss can be classified: (1) Prophylactic measures; (2) Early detection, graft surveillance; and (3) Intervention procedures aimed at saving the thrombosed graft.

Prophylaxis: Majority of transplant centers have adopted some type of routine prophylactic anticoagulation with various combinations of aspirin, unfractionated heparin, low molecular weight heparin and warfarin, with variable results but generally beneficial reducing the incidence of thrombosis[11].

There is currently no standard protocol consistently proven to prevent thrombosis following transplantation.

This prophylactic anticoagulation justifies that hemoperitoneum is the leading cause of surgical reintervention in the early postoperative period after pancreas transplantation.

Surveillance: Blood glucose monitoring in the early post-transplant period is especially useful to warn us about a possible vascular complication. Doppler ultrasound, CT angiography and magnetic resonance imaging (MRI) angiography have been used effectively in the early diagnosis of vascular graft complications. It is usual to perform imaging controls during the first days after pancreas transplantation with Doppler ultrasound[11]. If thrombosis is suspected, CT angiography or MRI angiography is performed to confirm the diagnosis and propose therapeutic options.

There are teams that perform CT angiography routinely in the early post-transplant period. These groups report higher thrombosis rates, including partial and asymptomatic thrombosis, which might not be detected with Doppler ultrasound[12].

Intervention: Partial venous thrombosis (usually of the splenic vein) has been managed successfully only with complete therapeutic anticoagulation[11,12]. However, complete portal thrombosis usually results in graft loss, although successful surgical and radiological rescues have been reported[13,14]. Radiological surveillance is critical in the early diagnosis of partial thrombosis, which can often be saved by therapeutic anticoagulation.

Due to the change in the donors profile, more transplants are currently performed with risk factors known as age, obesity, stroke as the cause of death and the donor in asystole. In this type of expanded donors, it is important not to add any more risk factors during the extraction, minimize the ischemia time and discard high thrombotic risk recipients detected during the pre-transplant evaluation, mainly thrombophilia,
Table 1 Summarizes these risk factors

| Thrombosis risk factor in pancreas transplantation |
|--------------------------------------------------|
| **Donor**                                        |
| Donor > 50 years old                             |
| Cerebrovascular cause of death                   |
| Prolonged cardiac arrest in the donor            |
| Donors after circulatory death (Maastricht 2 and 3) |
| Prolonged hypotension periods                    |
| Obesity                                          |
| Important arteriosclerosis in the celiac trunk   |
| **Extraction and preservation of pancreas:**     |
| Vascular abnormalities                           |
| Vascular injury during extraction (dorsal pancreatic artery) |
| Preservation solution (type, volume and perfusion pressure) |
| Ischemia time (warm and cold)                    |
| **Recipient:**                                   |
| Severe arteriosclerosis in the iliac vessels     |
| Age > 55 years old                               |
| Isolated transplant or pancreas transplant after kidney |
| Anticoagulant therapy established                |
| Thrombophilia                                    |

advanced arteriosclerosis and pancreas alone transplant.

HEMORRHAGE

Unlike other abdominal transplants, such as liver or kidney transplants, in which reoperations are rare, pancreas transplantation is subjected to a high rate of reoperations, which can be as high as 30%. Hemoperitoneum is the most frequent cause of reoperation in the immediate postoperative period\[^1\]. Fortunately, this event does not significantly affect graft survival. Bleeding represents less than 0.3% of early pancreatic graft losses. The incidence of hemoperitoneum is clearly related to the use of anticoagulation in the postoperative period. We need to distinguish between intra-abdominal, digestive and bladder haemorrhage.

**Intra-abdominal haemorrhage**

Most of the important hemoperitoneum that occurs in the early postoperative period has a surgical cause, in relation to peripancreatic vessels or vascular anastomosis, enhanced by the antithrombotic prophylaxis\[^1\]. The meticulous preparation of the duodenopancreatic graft during bench surgery can help to prevent most of these bleedings.

Once intra-abdominal bleeding has been diagnosed, we must correct any coagulation abnormality and suspend prophylactic heparin. If bleeding persists, surgical exploration would be indicated. In a recipient with hemodynamic instability we should not delay relaparotomy.

Possible causes of late intra-abdominal haemorrhage are ruptures of a fungal pseudoaneurysm, rupture of an arterial aneurysm or an arteriovenous fistula. The treatment of choice is endovascular, either by embolization or by stent\[^1\].

**Digestive haemorrhage**

Early digestive bleeding usually comes from the digestive anastomosis or the staple line of the duodenal ends. They are usually self-limited bleeding that responds to...
conservative measures (correction of coagulation abnormalities, heparin withdrawal and transfusion). If conservative measures do not solve the bleeding, the surgical revision is indicated.

**Bladder haemorrhage**

Early post-transplant haematuria is common in patients with bladder drainage and it is usually self-limited. In some cases, it is necessary to establish a continuous irrigation of the bladder.

**PANCREATITIS**

Early pancreatitis after a pancreas transplant occurs in 10%-20% of patients\[^{19}\]. It is specially associated to ischemia-reperfusion damage to the transplanted organ. Other less frequent causes involved are acute rejection and technical problems, especially if they affect ductal integrity\[^{7}\].

High serum amylase levels and graft edema are characteristic. Most ischemia-reperfusion pancreatitis are mild and progress favourably in the first days of the postoperative period. From an analytical point of view, the serum amylase peak due to ischemia-reperfusion damage occurs within the first 24-48 h after transplantation and rapidly evolves towards normalization\[^{20}\].

Regarding to imaging tests (CT and MRI), most recipients present in the immediate post-transplant period signs of mild pancreatitis that include graft enlargement, a thin ring of peripancreatic fluid and minimal peripancreatic fat infiltration.

Pancreatitis due to acute rejection usually results in a later elevation of serum amylase, from the fifth day after the transplantation. They are usually accompanied by data on acute rejection in the renal graft. The intensification of immunosuppression controls these immunological pancreatitis in most cases.

Complications of severe graft pancreatitis include pancreatic abscesses, sterile or infected pancreatic necrosis, pancreatic fistulas and pseudocysts. Severe pancreatitis is an important complication not only because it is commonly associated with infection, but also because it is a major risk factor for graft thrombosis\[^{7}\].

Currently, graft losses associated with severe pancreatitis and its complications do not exceed 0.6% of pancreas transplants.

However, determining the true incidence of severe graft pancreatitis is difficult because of the lack of a commonly accepted definition. There is not a classification for graft thrombosis, like Atlanta classification for native pancreatitis.

Another key point is that severe pancreatitis is frequently associated with infection and it is difficult to determine which one of this two complications appeared first. The united network for organ sharing Pancreas Transplant Registry does not even name pancreatitis as a separate cause of technical failure itself, but along with infection.

Risk factors for pancreatitis include donor risk factors (hemodynamic instability, vasopressor administration, obesity, age), injuries during multiorgan extraction, reperfusion damages (excessive volume infusion or excessive perfusion pressure), preservation injuries associated with an extended preservation time.

Although relatively rare, technical surgical problems can cause narrowing of the pancreatic duct. Another cause that produces obstruction of the pancreatic duct is urinary reflux when we use a bladder drainage. Rarer causes of pancreatitis include complications of a biopsy or bacterial and viral infections (for example cytomegalovirus).

Graft pancreatitis is suspected when elevated serum amylase and lipase are detected, and the recipient complains of abdominal pain where the graft is located. In severe pancreatitis, patients usually present other clinical symptoms like nausea, vomiting and ileus.

In some cases of graft pancreatitis, recipients may be hemodynamically instable and may even develop an adult respiratory distress syndrome. In grafts with bladder drainage, urinary amylase decreases markedly during episodes of pancreatitis. However, the endocrine graft function is often preserved, even in cases of severe pancreatitis, and only requires exogenous insulin when parenteral nutrition is administered.

The severity of pancreatitis is defined by laboratory data, including leukocytosis, hypocalcemia and elevated C-reactive protein. The degree of pancreatic inflammation or necrosis is assessed with abdominal CT. Abdominal MRI is less useful than CT in this context.

The treatment of pancreatitis is dictated by the treatment of the underlying cause.
Severe ischemia-reperfusion pancreatitis is usually treated with intestinal rest and nasogastric tube placement. Occasionally, parenteral nutrition is necessary. The use of octreotide to treat post-transplant pancreatitis has been suggested, but there is no clear evidence of its benefit. In cases of severe graft pancreatitis that endanger the patient’s life, due to the association of serious complications such as adult respiratory distress syndrome or septic shock, graft pancreatectomy is indicated. When pancreatic duct obstruction is the cause of the pancreatitis, a reoperation is required, and it will frequently be necessary to perform a pancreatectomy.

Reflux pancreatitis in recipients with bladder drainage is easily diagnosed and treated with the placement of a foley catheter. Repeated episodes of reflux pancreatitis in recipients with bladder drainage, is an indication of conversion to enteric drainage. Any peripancreatic infection associated with pancreatitis (e.g., peripancreatic abscess) has an indication of interventional radiology drainage, as well as an adequate antibiotic treatment.

Given the complications associated with severe acute graft pancreatitis, it is important to reduce its incidence by avoiding the known risk factors of the donor, mainly hemodynamic instability and obesity, as well as reducing the graft ischemia time as much as possible.

CONCLUSION

In this review we analyze three of the most important and frequent complications that occur in the early postoperative period after pancreas transplantation. Thrombosis justifies most of early graft losses. Performing a detailed surgical technique, minimizing risk factors in the donor and recipient, as well as using the appropriate antithrombotic protocol can lead to minimize the rate of thrombosis.

Postoperative haemorrhage justifies most of the reoperations but does not usually trigger graft loss. A balance needs to be struck between anticoagulation to prevent graft thrombosis and a reasonable reoperation rate. Meticulous haemostasis at the end of the procedure is essential to decrease the bleeding rate.

Finally, posttransplant pancreatitis, usually mild, related to ischemia-reperfusion, usually has a favorable course. A small percentage associates reoperations and graft loss. Minimizing the ischemic time and avoiding associating risk factors reduces its incidence.

REFERENCES

1 Finger EB, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matus AJ, Pruett TL, Kandaswamy R. A composite risk model for predicting technical failure in pancreas transplantation. *Am J Transplant* 2013; 13: 1840-1849 [PMID: 23711225 DOI: 10.1111/ajt.12269]

2 Troppmann C. Complications after pancreas transplantation. *Curr Opin Organ Transplant* 2010; 15: 112-118 [PMID: 20009931 DOI: 10.1097/MOT.0b013e3283355349]

3 Kopp WH, van Leeuwen CAT, Lam HD, Huurman VAL, de Fijter JW, Schaapherder AF, Baranski AG, Braat AE. Retrospective study on detection, treatment, and clinical outcome of graft thrombosis following pancreas transplantation. *Transpl Int* 2019; 32: 410-417 [PMID: 30525250 DOI: 10.1111/tri.13384]

4 Hakeem A, Chen J, Iype S, Cлатworthy MR, Watson CJE, Godfrey EM, Upsoni S, Saeb-Parsy K. Pancreatic allograft thrombosis: Suggestion for a CT grading system and management algorithm. *Am J Transplant* 2018; 18: 163-179 [PMID: 28719059 DOI: 10.1111/ajt.14433]

5 Mathusamy AS, Giangrande PL, Friend PJ. Pancreas allograft thrombosis. *Transplantation* 2010; 90: 705-707 [PMID: 20616765 DOI: 10.1097/TP.0b013e3181eb2ea0]

6 Morgan TA, Smith-Bindman R, Harbell J, Kornak J, Stock PG, Feldstein VA, US Findings in Patients at Risk for Pancreas Transplant Failure. *Radiology* 2016; 280: 281-289 [PMID: 26807892 DOI: 10.1148/radiol.2015150437]

7 Montiel-Casado MC, Fernández-Burgos I, Pérez-Daga JA, Aranda-Narváez JM, Sánchez-Pérez B, González-Sánchez AJ, Caballo-Díaz M, Burgos-Rodríguez D, Hernández-Marrero D, Santoyo-Santoyo J. Impact of blood amylase peak over vascular graft thrombosis in pancreas transplantation. *Transplant Proc* 2012; 44: 2627-2630 [PMID: 23146477 DOI: 10.1016/j.transproceed.2012.09.103]

8 Axeldrood DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010; 10: 837-845 [PMID: 20121753 DOI: 10.1111/j.1600-6143.2009.02996.x]

9 Fischereder M, Göhring P, Schneeberger H, Lohse P, Von Appen K, Samtleben W, Schlöndorff D, Land W. Early loss of renal transplants in patients with thrombophilia. *Transplantation* 1998; 65: 936-939 [PMID: 9565098 DOI: 10.1097/00007890-199804150-00013]
Adrogué HE, Matas AJ, McGlennon RC, Key NS, Gruessner A, Gruessner RW, Humar A, Sutherland DE, Kandaswamy R. Do inherited hypercoagulable states play a role in thrombotic events affecting kidney/pancreas transplant recipients? *Clin Transplant* 2007; 21: 32-37 [PMID: 17302589 DOI: 10.1111/j.1399-0012.2006.00574.x]

Harbell JW, Morgan T, Foldstein VA, Roll GR, Posselt A, Kang SM, Feng S, Hirose R, Freise CE, Stock P. Splenic Vein Thrombosis Following Pancreas Transplantation: Identification of Factors That Support Conservative Management. *Am J Transplant* 2017; 17: 2955-2962 [PMID: 28707821 DOI: 10.1111/ajt.14428]

10 Ciancio G, Cespedes M, Olson L, Miller J, Burke GW. Partial venous thrombosis of the pancreatic allografts after simultaneous pancreas-kidney transplantation. *Clin Transplant* 2000; 14: 464-471 [PMID: 11048991 DOI: 10.1034/j.1399-0012.2000.140504.x]

11 Gilbert R, Fernández-Cruz L, Real MI, Ricart MJ, Astudillo E, Montañá X. Treatment and outcome of pancreatic venous graft thrombosis after kidney--pancreas transplantation. *Br J Surg* 2002; 89: 355-360 [PMID: 11872064 DOI: 10.1046/j.0007-1323.2001.02016.x]

12 Fridell JA, Mangus RS, Mull AB, Taber TE, Sanders CE, Slisher RC, Goble ML, Powelson JA. Early reexploration for suspected thrombosis after pancreas transplantation. *Transplantation* 2011; 91: 902-907 [PMID: 21301398 DOI: 10.1097/TP.0b013e3182106069]

13 Han K, Ko HK, Tsauo J, Shin DJ, Kim Y, Ko GY, Han DJ, Shin S, Kim YH. Endovascular Management for the Treatment of Pancreas Transplant Venous Thrombosis: A Single-Center Experience. *J Vasc Interv Radiol* 2016; 27: 882-888 [PMID: 27107981 DOI: 10.1016/j.jvir.2016.02.022]

14 Laurence JM, Catral MS. Techniques of pancreas graft salvage/indications for allograft pancreatectomy. *Curr Opin Organ Transplant* 2016; 21: 405-411 [PMID: 27058314 DOI: 10.1097/MOT.0000000000000318]

15 Scheffert JL, Taber DJ, Pilch NA, Chavin KD, Baliga PK, Bratton CF. Clinical outcomes associated with the early postoperative use of heparin in pancreas transplantation. *Transplantation* 2014; 97: 681-685 [PMID: 24285337 DOI: 10.1097/TP.0b013e3182655.5d]

16 Montenegro M, Vaidya S, Bakhthavatsalam R, Halldorson J. Pseudoaneurysm after combined kidney/pancreas transplantation presenting with sentinel bleeding: a case report and review. *Ann Transplant* 2014; 19: 317-319 [PMID: 24995594 DOI: 10.12659/AOT.890356]

17 Moya-Herraiz A, Muñoz-Bellvis L, Ferrer-Fábrega J, Manrique Municio A, Pérez-Daga JA, Muñoz-Casares C, Alarcó-Hernández A, Gómez-Gutiérrez M, Casanova-Rituerto D, Sanchez-Bueno F, Jimenez-Romero C, Fernández-Cruz Pérez L. Cooperative Study of the Spanish Pancreas Transplant Group (GETP): Surgical Complications. *Cir Esp* 2015; 93: 300-306 [PMID: 25635111 DOI: 10.1016/j.ciresp.2014.12.006]

18 Leone John P, Christensen K, Bhargava R, Hunter DW, Troppmann C, Lazarov V, Dunn DL, Paraskevas S, Coad JE, and Gruessner RWG. Postoperative management. In: *Transplantation of the Pancreas*. New York: Springer, 2004: 279-266 [DOI: 10.1007/978-1-4757-4371-5_5]
