Pancreas transplantation: an overview

Atualização no transplante de pâncreas

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ABSTRACT

Pancreas transplantation is the only treatment able to reestablish normal glucose and glycated hemoglobin levels in insulin-dependent diabetic patients without the use of exogenous insulin. The evolution of pancreas transplantation in treatment of diabetes was determined by advances in the fields of surgical technique, organ preservation and immunosuppressants. The main complication leading to graft loss is technical failure followed by acute or chronic rejection. Technical failure means graft loss within the first three months following transplantation due to vascular thrombosis (50%), pancreatitis (20%), infection (18%), fistula (6.5%) and bleeding (2.4%). Immunological complications still affect 30% of patients, and rejection is the cause of graft loss in 10% of cases. Chronic rejection is the most common late complication. Cardiovascular diseases are the most common causes of late mortality in pancreas transplantation, so it remains the most effective treatment for type 1 diabetes patients. There is a significant improvement in quality of life and in patient's survival rates. The development of islet transplantation could eliminate or minimize surgical complications and immunosuppression.

Keywords: Pancreas transplantation/adverse effects; Immunosuppression; Islets of Langerhans transplantation

RESUMO

O transplante de pâncreas é o único tratamento capaz de restabelecer os níveis de glicose e hemoglobina glicada em pacientes diabéticos dependentes de insulina, sem o uso de insulina exógena. A evolução do transplante de pâncreas no tratamento de diabetes foi marcada por avanços nos campos da técnica cirúrgica, preservação de órgãos e imunossupressão. A principal complicação da perda do enxerto é a falha técnica, seguida de rejeição aguda ou crônica. Por falha técnica entende-se perda do enxerto dentro dos primeiros três meses seguintes ao transplante devido a: trombose vascular (50%), pancreatite (20%), infecção (18%), fístula (6,5%) e hemorragia (2,4%). Complicações imunológicas ainda afetam 30% dos pacientes, e a rejeição causa perda do enxerto em 10% dos casos. A rejeição crônica é a complicação tardia mais comum. Doenças cardiovasculares são a causa mais frequente de mortalidade tardia no transplante de pâncreas que continua sendo o tratamento mais eficaz para pacientes com diabetes do tipo 1. Há uma importante melhora na qualidade de vida e na sobrevida dos pacientes. O desenvolvimento de ilhotas transplantadas pode eliminar ou minimizar complicações cirúrgicas e a imunossupressão.

Descritores: Transplante de pâncreas/efeitos adversos; Imunossupressão; Transplante das ilhotas pancreáticas

INTRODUCTION

Diabetes mellitus (DM) affects 6% of the working population. The most common complications are related to vascular, renal and ophthalmologic diseases, and affect 50% of insulin-dependent diabetic patients within a 20-year span[1].

Pancreas transplantation (PTx) is the only treatment able to reestablish normal glucose and glycated hemoglobin levels in insulin-dependent diabetic patients without the use of exogenous insulin[2]. This can be achieved by transplanting the whole pancreas or by transplant of islet cells, the later still under study. The evolution of PTx in DM treatment has been determined by advances in the fields of surgical technique[3], organ preservation and immunosuppressants[4].

PTx can be performed in three different categories: pancreas transplant alone (PTA), pancreas after kidney transplantation (PAK) or simultaneous pancreas/kidney transplantation (SPK). The most common type is SPK for insulin-dependant DM patients with kidney failure. PAK is performed in patients who were previously submitted to renal transplantation. PTA is performed

in type I DM patient with recurrent non-symptomatic hypoglycemia episodes or hyperlabile DM[4].

Patients' quality of life improves immensely after PTx. It avoids episodes of hypoglycemia or ketoacidosis, stops daily subcutaneous injections of insulin or frequent punctures to monitor glycemia and change diet restrictions. It also prevents DM complications and protects the transplanted kidney[2].

Regarding secondary DM complications, PTx may lead to partial regression of neuropathy[5], stabilization of retinopathy[6], and regression of the damaged structure of the native kidney in PTA[7]. It may also prevent DM-induced nephropathy in the transplanted kidney in SPK[8].

There is a theoretical advantage to the islet cell transplantation when compared to the whole organ procedure. However, islet cell transplantation is still an experimental procedure, performed only on clinical studies.

Patient selection

Patients with DM nephropathy leading to kidney failure are eligible to SPK. Such patients with functioning kidney graft are candidates to PAK. Indeed, these patients are already on immunosuppression and the surgical procedure represents the only risk. PTA is performed in rare occasions, when there is no DM-induced kidney failure, but the clinical control of DM with exogenous insulin is not effective, leading to recurrent acute metabolic complications that require medical treatment, such as asymptomatic hypoglycemia and ketoacidosis[9].

The current patient selection criteria are:
- type 1 DM;
- age between 18 and 55 years;
- absence of systemic DM secondary complications;
- non-renal organic insufficiency;
- no neoplastic disease;
- emotional and social stability;
- no immunosuppression contraindication.

Proliferative retinopathy, iliac arteries obstruction, clinical autonomic neuropathy, HIV-positive and positive T-cell test are relative exclusion criteria.

Absolute exclusion criteria to the procedure are heart failure, severe pulmonary insufficiency, social or emotional instability, active infection or sepsis, neoplastic disease and obesity BMI > 30 kg/m².

Donor selection

Adequate management of possible donors is paramount to avoid graft complications. Hemodynamic and glycemic instability must be avoided.

Selection criteria are not only based on ABO blood system, but also on negative crossmatching and other criteria, such as age between 10 and 50 years, body mass index (BMI) between 15 and 40 and absence of DM[10].

The macroscopic evaluation of the pancreas in donor surgery is important and may be the reason to use or not the graft. The surgeon should look closely for signs of pancreatitis, areas of steatonecrosis, excessive glandular edema, hematoma, fat infiltration, and cystic or solid nodular lesions.

Moreover, previous duodenal, pancreatic or spleen surgery, malignancy, infectious diseases (HIV, B or C virus hepatitis and HTLV), chronic hepatic disease and alcoholism must be excluded.

Transplant surgery

We must bear in mind that the kidney is usually transplanted in the same surgery. The kidney is implanted before the pancreas, because the more delicate organ is less harmed by surgical manipulation. The standard surgical access is throughout an abdominal midline incision. It is preferred to implant the pancreas on the right side as iliac vessels are easily accessed by this side.

The graft blood drainage may be systemic or portal. The first is easily performed but the latter is more physiological, since insulin firstly reaches the liver and only then goes to the systemic circulation. However, glucose metabolism in both techniques is similar and there is no difference in patient and graft survival[11].

The exocrine secretions of the pancreas may drain to the bladder or bowel. In the past, bladder drainage was preferred since graft rejection could be monitored by urinary amylase level. Indeed, most PTx are SPK and rejection episodes are monitored through kidney function. In addition, enteric drainage is more physiologic and has no urinary complications or metabolic complications. Therefore, enteric drainage is now preferred in SPK.

Before the transplant surgery itself, the pancreatic graft is procured *en bloc* with the spleen, undergoes a back table surgery when a splenectomy and a Y-vascular anastomosis of the superior mesenteric and the splenic arteries are performed with external and internal iliac grafts (Figure 1).

The main surgical steps are summarized below:
1. laparotomy;
2. bladder exposure (only if bladder drainage);
3. terminal ileum and cecum cranial mobilization;
4. iliac vessels dissection and mobilization, with ligature of right iliac internal veins;
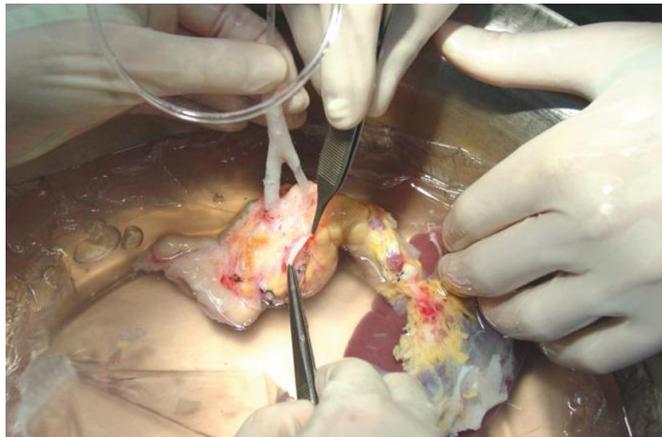
Figure 1. Back-table surgery when a splenectomy and a Y vascular anastomosis of the superior mesenteric and splenic arteries are performed with external and internal iliac graft.

5. graft portal vein termino-lateral anastomosis to the patient's right common iliac vein (systemic drainage);
6. graft artery termino-lateral anastomosis to the patient's right common iliac artery;
7. exocrine graft secretion drainage urinary (latero-lateral bladder-duodenum anastomosis) or enteric (latero-lateral ileum-duodenum anastomosis);
8. abdominal cavity hemostasis;
9. abdominal wound closure.

Immunosuppression

The most frequently used immunosuppressive protocols are based on induction and maintenance phases. Induction drugs are monoclonal antilymphocytes, such as T cell antibodies (OKT3), or polyclonal such as thymoglobulin (ATG); or even anti IL-2 receptor antibodies (basiliximab and daclizumab). Maintenance is based upon the utilization of a calcineurin inhibitor (tacrolimus) associated with anti-metabolic agents (micophenolate mofetil) and corticosteroids (prednisone).

Transplantation results

According to data from the Organ Procurement and Transplantation Network (OPTN), in the past 21 years (1988 to February 2010) a total of 16,824 SPK and 6,593 PTA + PAK were performed in the United States. The survival rate of SPK patients in the United States is 95% in the first year, 90.4% in the first three years and 86.1% in the first five years. Graft survival rates are of 91.7%, 84.5% and 76.7%, respectively, for the same periods[12].

The patient and survival rates are lower in the other two PTx types. PTA and PAK have patient survival rates of 94% in the first year, 89% in the first three years and 82% in the first five years; and graft survival rates of 77%, 63.8% and 51% for the same time periods. Male patients show better patient and graft survival rates[12,13].

Complications

The main complication leading to graft loss is a technical failure followed by acute or chronic rejection. A technical failure is the graft loss within the first three months following transplantation due to vascular thrombosis (50%), pancreatitis (20%), infection (18%), fistula (6.5%) and bleeding (2.4%). In PAK and PTA, patients' rejection is the main cause of graft loss[14,15].

Intestinal leaks are one of the most serious PTx complications and are found in 5-8% of patients. It generally occurs immediately after surgery and is related to blood perfusion deficit and ischemia. In most cases, graft removal is the only treatment to this condition[16,17].

Bladder drained PTx, in which exocrinous graft secretions are directed to the bladder, tend to lead to metabolic and urological complications. The most frequent are hematuria, urinary tract infections, urethritis, bladder calculi, and bladder leaks. In such cases, a surgery should be performed to convert the bladder to enteric drainage[15].

Immunological complications still affect 30% of SPK patients and rejection is still the cause of graft loss in 10% of cases. The criteria for graft rejection diagnosis are blood creatinine elevation (for SPK), lowering of urinary amylase (for bladder drainage patients), blood lipase elevation, and pancreas biopsy (gold standard)[2].

Infections are still the main cause of death in PTx patients when related to the procedure. They are most commonly bacterial and affect the abdominal wall and the urinary tract. Patients who underwent PTx have a higher risk to develop CMV infection, and it occurs in 25% of all cases. Fungal infections are difficult to treat and are associated with high death rates. *Aspergillus* and *Criptococcu*s are the most common agents[18-21].

Neoplasia is a rare complication in PTx. It is more fatal in this procedure when compared to other solid organ transplantation. It is potentially related to immunosuppression and CMV[22].

Chronic rejection is the most common late complication. Also, cardiovascular diseases are the most common causes of late mortality in PTx.

CONCLUSION

Pancreas transplantation is still the most effective treatment for type 1 DM patients. There are surgical complications and immunosuppression is mandatory.

However, based on patient's survival rates following PTx, there is a significant improvement in the quality of life and in kidney failure.

PTA is the appropriate treatment to complicated DM patients without kidney failure and must be performed according to the American Diabetes Society guidelines. The development of islet transplantation could eliminate or minimize surgical complications and immunosuppression.

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