Pancreas transplantation in Lyon: overall results

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Summary. A total of 182 pancreatic transplantations were performed between 1976 and 1990. Survival of the grafts was 45% at 5 years. Major causes of graft loss have been rejection and venous thrombosis. Death occurred in 24 patients and was usually related to vascular complications. The techniques of duodenopancreatic transplantation with enteric drainage, bladder drainage and the technique of segmental duct obstructed grafts were compared. A higher rate of surgical complications was observed with enteric drainage, whereas it is unclear from the data whether segmental grafts or duodenopancreatic grafts drained into the bladder lead to different results.

Key words: Transplantation-Pancreas-Duct obstruction-Enteric drainage- Bladder drainage

Introduction

A pancreas transplantation programme was started in Lyon in 1976 using the technique of segmental grafting with neoprene injection. This technique was originally described by Dubernard et al. (1976) in animals. Exocrine secretion of the gland is blocked by intra-ductal injection of a synthetic polymer that solidifies when in contact with pancreatic secretions. This technique appeared to be very convenient as it eliminates the need for diversion of the pancreatic secretions in another organ which can induce surgical complications. In addition this technique could be associated with segmental harvesting of the gland, thereby simplifying organ removal.

This technique has been used extensively in Lyon and in many other groups in the seventies and early eighties. In fact the need for massive immunosuppression and especially steroid therapy caused many surgical complications such as fistulas when enteric drainage of the pancreatic secretions was used. In the mid eighties cyclosporin A allowed other techniques of enteric drainage to be utilized as well as techniques of bladder drainage of the pancreatic secretion (Mac Donald 1982).

In our institution, after extensive use of the segmental injection technique until 1986, we have tested other techniques such as whole pancreas transplantation with enteric drainage, and later, whole organ transplantation with bladder drainage.

Our objective is to compare the different types of techniques in terms of the mass of tissue and the type of management of the exocrine secretion.

Subjects and methods

Our study involved 182 patients with type 1 diabetes mellitus who had received pancreas transplants. General data concerning characteristics of the patients are summarized in Table 1. Data concerning age, mean duration of diabetes, presence of dialysis or ophthalmologic complications were identical in all patients whereas data concerning vascular complications (macroangiopathy, cardiac complications, amputations) showed an improvement of the status of the patients probably due to better care for the diabetic patients and better selection in the latest series.

The technique used for the first 55 patients was segmental transplantation with neoprene injection (from 1976 to 1985). Then we performed a comparative trial between segmental grafts and total duodeno-pancreatic grafts with enteric diversion (33 patients), followed by a series of 33 consecutive segmental injected grafts, and then another comparative series between segmental injected grafts and total duodeno-pancreatic grafts this time drained into the bladder (67 patients).

Immunosuppression varied from 1976 to 1990 and six different protocols were used: **Protocol A**: azathioprine (2–3 mg · kg⁻¹ · day⁻¹), prednisone (1 mg · kg⁻¹ · day⁻¹ for 10 days then decrease), antilymphocyte globulin 4 to 12 weeks; **Protocol B**: cyclosporin A 8 mg · kg⁻¹ · day⁻¹ and antilymphocyte globulin 8 to 12 weeks; **Protocol C**: identical to protocol A plus cyclosporin starting 4 to 6 weeks post-operatively; **Protocol D**: azathioprine (2 to 3 mg · kg⁻¹ · day⁻¹), Prednisone 0.25 mg · kg⁻¹ · day⁻¹ and cyclosporin (6–8 mg · kg⁻¹ · day⁻¹); **Protocol E**: azathioprine (2–3 mg · kg⁻¹ · day⁻¹), prednisone 0.25 mg · kg⁻¹ · day⁻¹, cyclosporin 4–6 mg · kg⁻¹ · day⁻¹ and antilymphocyte globulin or OKT3 for 14

days ; **Protocol F** : azathioprine ($2\text{--}3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), prednisone ($0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), cyclosporin ($4\text{--}6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and antilymphocyte globulin ; **Protocol G** : azathioprine ($2\text{--}3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), prednisone ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 2 weeks then decrease to $10\text{--}15 \text{ mg} \cdot \text{day}^{-1}$), cyclosporin $4\text{--}6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ and antilymphocyte globulin for 14 days. Patients were followed post-operatively and neuropathy, ophthalmologic complications, control of diabetes have been studied and are reported elsewhere in this issue. Results are expressed in terms of surgical complications and graft losses.

Results

Overall results

Overall results show that the number of functioning grafts is 74 after 182 performed. Results in terms of the period of transplantation and the immunosuppression are shown in the figure. Graft losses were : rejection (39 cases), venous thrombosis (28 cases) arterial thrombosis (14 cases), or surgical complications such as pancreatitis of the graft, haemorrhage (3 cases).

Rejection was observed less frequently with improvement of the immunosuppression as shown in Figure 1. For diagnosis of pancreas rejection, kidney rejection was employed as a marker. The use of urinary amylases in the latest group of patients with bladder drainage was disappointing in this regard.

Venous thrombosis was a major cause of graft loss in our series. The incidence of this complication decreased markedly since 1988, after University of Wisconsin solution was used routinely in our institution (Wahlberg 1987). However the rate of thrombosis was still significant in 1989 (3/29) and in 1990 (3/31). Death was observed in 24 cases. Death was related in most cases to cardiovascular complication such as myocardial infarction or cerebro-vascular obstruction.

Surgical techniques

Surgical complications according to the technique used were especially studied. When comparing segmental duct obstructed grafts (DO) vs whole organ with enteric drainage (ED), the number of surgical complications requiring re-operation was higher in the group of patients with enteric drainage (6 vs 1); however the number of graft losses was identical in both groups (6 vs 5). The main causes of loss of pancreatic graft function in this comparative trial was : early vascular thrombosis (two grafts lost in DO group and three in ED group) and rejection : one graft was lost from rejection at 8 months in DO group in a patient with irreversible kidney rejection 2 months after transplantation. Two rejection episodes occurred in ED group : in the first patient 34 months after transplantation (the kidney was lost from rejection 20 months after double transplantation). In the second patient both organs were rejected 14 months after transplantation

One patient in DO group died with a functioning graft 5 months after transplantation (necrotizing enteritis) and two

Table 1. Characteristics of the 182 patients receiving a pancreas transplant in Lyon

	1976-1985	1985-1990
Age (years(SD))	37.2(11)	36.9(7,6)
Duration of diabetes (years(SD))	22.0(2,5)	23.9(1,6)
Dialysis (n)	46	111
Dial. Duration (months(SD))	10.0(2)	16(6)
Retinopathy (n)	51	127
Macroangiopathy	40	31
Myocardiopathy	24	38
Neuropathy(n)	55	127

transplantectomies were necessary : one for a major post-operative bleeding in DO group and the other for an extensive pancreatic necrosis probably due to a prolonged cold ischaemia in the ED group. Twelve DO (71%) and eight ED (57%) pancreatic grafts are still functioning and all these patients are insulin-independent except one (with DO graft) requiring insulin therapy (30 % of pre-transplant dose) despite a preserved C-peptide secretion. Complications requiring iterative surgery were more frequent in the ED group : one enteric leakage, two small bowel occlusions, one post-operative bleeding and two wound dehiscences were observed in the ED group. In the DO group only one wound dehiscence and one post-operative bleeding occurred.

Our present results in the trial comparing bladder drainage (BD-25 patients) and segmental duct obstructed (DO-26 patients) grafts are the following : venous thrombosis : 2 in BD vs 5 respectively ; surgical condition requiring iterative surgery : 2 in BD vs 1, wound infection 14 in ED vs 4, pancreatic fistula 2 vs 2 ; bladder fistula 2 in BD vs 0 ; Urologic complication episodes (Urinary tract infection 65 episodes in BD vs 45 in ED, chronic retention 3 in BD vs 1 in DO, chemical cystitis 2 in BD) were significantly more frequent in the BD group. Loss of pancreatic grafts and of kidney grafts were identical in both groups (6 and 6 ; 3 and 2, respectively)

Actuarial survival rates are at present 61 in the BD group versus 57 in the DO group at 2 years.

Discussion

Overall survival of pancreas transplants is 45 % at 5 years, most transplant loss occurs during the first 2 years ; global survival does not seem to be influenced by the technique. Function of the grafts is similar whatever the technique used. However more diabetic-type glucose tolerance tests were found in a small group of patients with segmental grafts as compared to total grafts with enteric diversion. (La Rocca 1988). Similar findings were not found in our latest tests in this series or in the series

of total grafts drained in the bladder. Data from the International Registry of Pancreatic Transplantation found a difference of graft function according to the technique.

Longer follow-up will determine which technique has the best functional results and the lower rate of surgical complications.

Fig.1. Survival of the pancreatic graft according to the protocol of immunosuppression used (A, B, C, D, E, F and G)

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