CHAPTER 8

Pancreatic Transplantation Using the Duct Occlusion Technique

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Insulin-dependent diabetes mellitus leads to deleterious late vascular complications. This fact accounts for higher morbidity and mortality compared to a non-diabetic population. Experimental studies (1, 2) proved and preliminary clinical data (3, 4) suggest that transplantation of the pancreas may prevent these late diabetic complications. Furthermore, since worldwide experience with pancreatic grafting has improved, we are encouraged to continue with human pancreas transplantation until the transplantation of isolated human islets becomes successful.

The following report presents the Munich experience with the simultaneous transplantation of the pancreas and kidney using the duct occlusion technique with prolamine. We will also discuss our experience, though limited, with the sole transplantation of the pancreas in nonuremic patients. Parts of our experience have been published elsewhere (5).

PATIENT SELECTION CRITERIA

Two groups of patients with type I diabetes were accepted for pancreatic grafting:

Group A:Patients with end-stage renal disease
(These patients received a pancreas and a kidney simultaneously)

Group B:Non-uremic diabetics with progressive retinopathy
(These patients only received a pancreas transplant)

Most of the patients in both groups suffered from other diabetic complications such as retinopathy, polyneuropathy and hypertension. Since 1985, patients with coronary heart disease or patients over 50 years of age have not been accepted for pancreatic grafting.

METHODS

Since 1979, we have performed 97 pancreas transplants in 93 diabetic patients. Eighty-six of these patients received a pancreas and a kidney simultaneously, 4 patients required retransplantation and 7 who underwent an isolated transplantation of the pancreas had no signs of end-stage renal disease (Table 1). For the handling of exocrine secretion, we used the duct occlusion technique with prolamine exclusively (5).

Table 1. Number of segmental pancreatic allotransplants performed at the Munich Transplant Center.

Period	No.	Transplantation
1979-1981 (Starting period)	3	Pancreas and Kidney
1981-8/1984	31	Pancreas + Kidney
(Cyclosporine era)	1	Pancreas regrafts
9/1984 - 8/1988	52	Pancreas + Kidney
	3	Pancreas regrafts
	7	Pancreas Alone
Total:	97	

Organ Harvesting

We only accepted organs from donors who were 10 to 50 years of age with stable circulation and normal or subnormal endocrine and exocrine function. In all cases, we harvested a segmental pancreas consisting

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of the corpus and tail. For anastomoses we resected the coeliac axis and the portal vein. Recently, in cases of multiple organ transplantation, we used the mesenteric superior vein and the splenic artery in interposition with the iliac artery of the donor. For the perfusion of the organs in situ, we used "Eurocollins" solution. Immunological selection was based upon blood group compatibility and a negative cross-match. Tissue typing was then performed retrospectively.

Figure 1. Ex vivo approach of duct occlusion with prolamine. The duct injection is considered to be efficient when first signs of over-injection appear by x-ray.

Duct Obliteration Procedure

Prior to transplantation, the pancreatic duct was cannulated with a hypodermic needle. About 3-5 ml of occlusive substance, i.e. prolamine "Ethibloc^{R}" (Ethicon, Norderstedt, FRG) was injected under X-ray control.

The duct obliteration was considered efficient when first signs of "over-injection" were verified on the X-ray (Fig. 1). Following occlusion, the ductal orifice and the parenchyma of the cut surface were ligated. The characteristics of prolamine are demonstrated in Table 2.

Recipient Operation

The main surgical technique and postoperative management are shown in Table 3. From 1979 until 1984, the graft was placed partly intra- and partly extraperitoneally, as described by Dubernard, et al (6).

Table 2. Characteristics of prolamine.

1. Solidifies rapidly in the duct system
2. Is microbiologically indifferent
3. Is reabsorbed within 2 weeks (in dogs)
4. Leads to necrosis and regeneration of the duct epithelium
5. Causes atrophy and fibrosis of the exocrine parenchyma
6. Is radiopaque
7. Does not affect endocrine function

Since September of 1984, grafts have been placed strictly intraperitoneally along the colon ascends. In the first 48 hours following transplantation, an abdominal irrigation of 6 liter CAPD solution daily was carried out. The anastomoses of the vessels were managed by means of the end-to-side technique between the donor's coeliac axis and portal vein and the recipient's external iliac vessels. Seven patients developed fatal bowel obstructions due to adhesions. These patients were treated without abdominal irrigation.

Prolamine Complications

In contrast to the animal experimental findings (7, 8) we have noted a more delayed destruction and atrophy of the exocrine parenchyma following duct occlusion with prolamine. During our experience with prolamine, every second patient developed a subcutaneous pancreatic fistula (9) with a high incidence of secondary infection (complicated fistula). In order to prevent the pancreatic fistulae, we introduced a strictly intraperitoneally positioning of the graft and an abdominal irrigation. We hypothesized a reduction of the incidence of fistulae via reabsorption of the highly active amylase/lipase secretions by the peritoneum.

Table 3. Surgical technique and postoperative management according to different periods.

Period	Surgical Technique	Anticoagulation therapy	Immunosuppressive therapy	Patient Selection
1979-9/1984 Group I n= 32	Extra-/Intra-Peritoneal Positioning	"High" dose Heparin (PTT: 60 SEC.)	CsA plus Steroids Maintenance: CsA-Monotherapy	CAD not excluded, Elderly pts Accepted
9/1984-8/1988 Group II n= 52	Strictly Intra-Peritoneal Positioning Plus Abdomen.lavage (2 days)	"Low" dose Heparin (PTT: 40 sec.) Plus Dextran 40	Triple/quadruple Drug Induction therapy Triple/ Double drug Maintenance therapy (CsA+AZA)	Exclusion of CAD (proven by arteriography) Pts > 50 years Not accepted

A pilot study, however, proved that this approach was unsuccessful since there was no reduction in the incidences of fistulae. More recently we have used fibrin tissue adhesive which is applied to the organ surface (10). The combination of the occlusion technique with the use of fibrin tissue adhesive and the abdominal irrigation actually seems to reduce the complications caused by transient exocrine secretions (Table 4).

Postoperative Management

Successful transplantation of the pancreas requires both a clear concept of postoperative management and the prevention of 2 major complications: the primary irreversible venous thrombosis and the irreversible rejection of the organ. In our opinion, this can best be accomplished by effective immunosuppression and anticoagulative measures for avoiding the risk of bleeding. The additional blocking of the exocrine function with "Somatostatin" may also be helpful.

Table 4. Incidence of fistula formation in relation to applied surgical techniques.

I	Extraperitoneal positioning of the graft	50% (n= 32)
II	Intraperitoneal positioning of the graft	70% (n= 7)
III	Intraperitoneal positioning of the graft, lavage	40% (n= 16)
IV	Intraperitoneal positioning of the graft, lavage and tissue adhesive	20% (n= 20)

Anticoagulative Measures

From 1979 to 1984, we only used heparin for anticoagulation with a targeted PTT value of 60-80 seconds. This regimen, however, induced severe hemorrhages requiring interventions. Since 1985, we have used a combined treatment of "Dextran^{R}" 40 and low-dose heparin, now targeting a PTT value of 40 seconds. When comparing the high-dose and low-dose heparin protocols, the rates of venous thromboses did not differ statistically, although the frequency of bleeding complications was reduced significantly.

Immunosuppressive Protocol

With increasing experience using cyclosporine (CsA), we have been confronted with the undesirable effects of this drug for it is associated with nephrotoxicity and has a narrow therapeutic range in terms of difficulty in achieving a maximum immunosuppressive effect with minimal nephrotoxicity.

The alloreactivity reaches its maximum immediately posttransplant following antigen exposition. As a consequence, we initiated new therapeutic approaches to provide the highest possible immunosuppressive index using CsA in a non-nephrotoxic dosage regimen. At

Table 5. Immunosuppressive protocol in pancreatic transplantation

Induction Therapy:	Quadruple Drug
CsA:	1 mg/ b.w. i.v. via perfusor/24h
AZA:	2-1 mg/ b.w.
Steroids:	500 mg/ day MP initially, tapered to 30 mg/ day within 1 week
ATG/ALG:	4 mg/ 20 mg/b/w/ for 10 days or
OKT3:	5 mg/ day for 10 days
Triple-drug maintenance:	CsA + AZA + Steroids for 6 months
Maintenance therapy:	Double drug (CsA + AZA)

present, our group has an established immunosuppressive protocol (Table 5) as follows:

Quadruple drug induction therapy; triple-drug maintenance treatment CsA, azathioprine (AZA), and steroids over a period of 6 months postoperatively then double-drug maintenance therapy (CsA, AZA) beyond 6 months posttransplant.

To date, 52 patients with simultaneous pancreas and kidney transplants have been treated according to the above mentioned regimen. The preliminary data are promising and have been published in Gothenburg (11). The overall losses of pancreas grafts are shown in Table 6.

Table 6. Pancreas graft loss following simultaneous pancreas and kidney

(Period: 9/1984 - 8/1988)		n=52
Venous thrombosis	15%	(n=8)
Infected fistula	12%	(n=6)
Parenchymal bleeding	2%	(n=1)
Acute rejection	10%	(n=5)
Chronic rejection	6%	(n=3)
Patient death	2%	(n=1)

RESULTS

Patients were divided into 2 groups:

Group I: Patients who received a transplant between 1979 and August 1984.

Group II: Patients who received a transplant between August 1984 and August 1988.

The patient survival rate in Group I was 82%. The graft function rates 3-years posttransplant were 25% for the pancreas and 33% for the kidney (Fig. 2).

The patient survival rate in Group II was 98% . The graft function rate 4-years posttransplant was 48% for the pancreas and 70% for the kidney (Fig. 3).

All survival rates were estimated by the computerized probability formula of Cutler/Ederer (12).

The results in patients receiving an isolated pancreas transplant were poor. Graft loss due to acute irreversible rejection was observed in 2 cases, progressive rejection was noted in 1 and 4 grafts were lost due to primary irreversible thrombosis.

Metabolic Studies

The endocrine function of the pancreas will subsequently be investigated in all successfully grafted patients with an oral glucose load and arginine-stimulation. None of the successfully transplanted patients re-

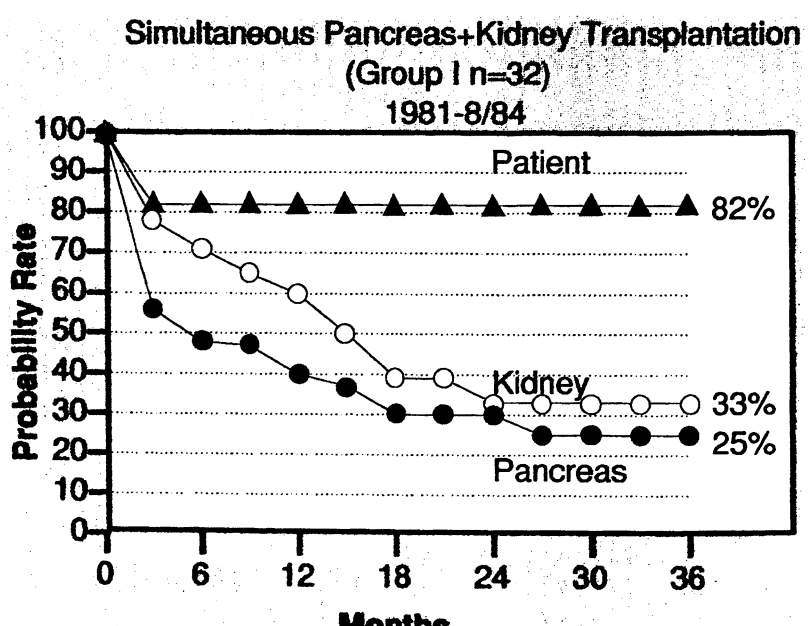

Figure 2. Patient and graft survival in simultaneous pancreas and kidney transplantation from 1981-8/1984. (Cutler/Ederer formula)

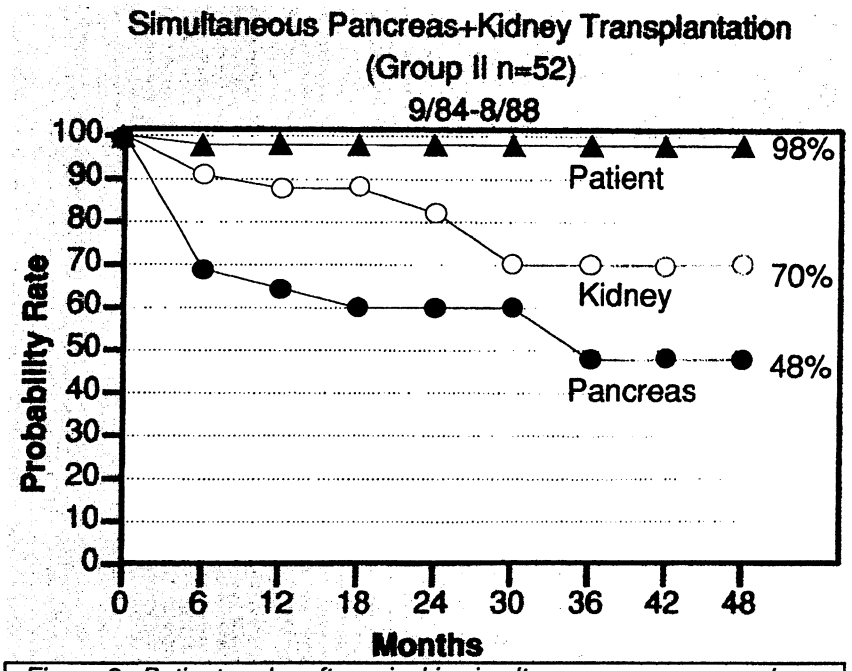

Figure 3. Patient and graft survival in simultaneous pancreas and kidney transplantation. According to modified surgical technique, immunosuppressive and anticoagulation therapy (9/1984 - 8/1988).

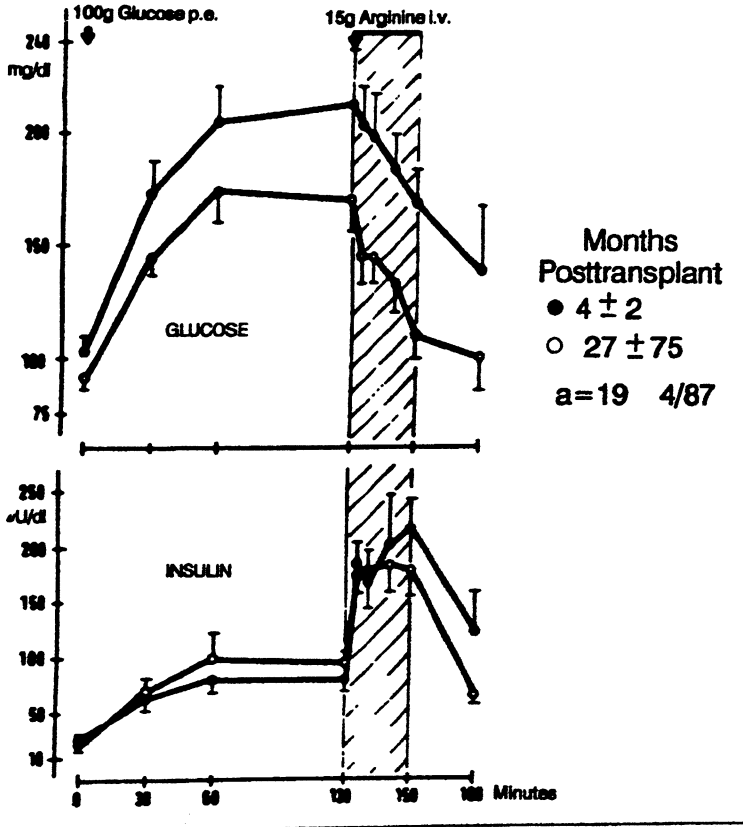

Figure 4. Behavior of blood glucose and serum insulin during oral glucose load and i.v. arginine stimulation (shaded area) according to different posttransplant periods in simultaneously transplanted patients.

quired exogenous insulin, all showed a normal glycosylated hemoglobin and 71% presented with normal oral glucose tolerance.

The remaining 29% of the successfully transplanted patients had impaired glucose disposal with lower and delayed insulin release. The most important observation regarding the technique used for duct occlusion was that in the long run, no deterioration of the endocrine function occurred (Fig. 4).

Ophthalmological and Neurological Observations

In 56% of 34 investigated patients, visual acuity improved. Stabilization was noted in 32% and deterioration was only observed in 12%. A regression and/or stabilization of vascular proliferation was observed in 88% whereas a progression occurred in 12% of the cases.

However, vitreous hemorrhage was reduced from 69% prior to transplantation to 24% posttransplant. In 28 patients observed, subjective signs of polyneuropathy such as paresthesias, hyper- and hyposthesia, restless legs or muscle weakness disappeared in 46%. No deterioration was observed. Sensory or motor nerve conduction velocity improved in 71% whereas no change occurred in 28% of the cases and no deterioration was observed.

Peripheral Microcirculation

To evaluate the influence of pancreas grafting on peripheral microcirculation, we measured the transcutaneous oxygen pressure ($tcpO_2$) and used telethermography (14).

The data from 18 patients showed a significant rise of $tcpO_2$ from values of 44 ± 2mm Hg pretransplant to 63 ± 4mm Hg posttransplant. The thermographic pattern also revealed a significant increase: the skin-temperature measured on the forefeet was +1.92 ± 0.07°C compared to 0.36 ± 0.020 °C in the non-diabetic kidney grafted patients.

SUMMARY

Since 1979, the Munich Group has gathered experience with 100 consecutive pancreas transplants using the duct occlusion technique. At the present time, 40 of the pancreas grafts (44%) and 56 of the renal grafts (65%) of 90 patients who received both a pancreas and a kidney are still functioning.

The mortality rate of 18% in the early period was relatively high. In the period from 1984 until 1988- using the simple transplantation technique - only one patient died. During this period, our overall results improved with the use of a modified surgical technique and different immunosuppressive and anticoagulative measures along with better patient selection. Normalization of the glucose metabolism seems to improve the rate of late diabetic complications. The duct occlusion technique in isolated pancreas transplants might have been a disadvantage in accounting for the poor results.

With regard to metabolic studies, there is now ample evidence to suggest that successful pancreatic transplantation leads to complete normalization of glucose metabolism including normoglycemia in more than 70% of all patients.

In addition, clinical data are accumulating that suggest successful pancreatic transplantation has a beneficial effect on the late secondary syndrome of Type I diabetes mellitus.

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