TRANSPLANTATION OF THE ENDOCRINE PANCREAS IN DIABETES MELLITUS

EDITORS

Reinout van Schilfgaarde, M.D.
Professor of Surgery and Chairman

Department of Surgery
University of Groningen and University Hospital Groningen
Groningen, The Netherlands

and

Mark A. Hardy, M.D.
Professor of Surgery and Director

Organ Transplantation, Department of Surgery
Columbia University, College of Physicians and Surgeons
New York, NY, USA

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Contents

Chapter III: RECOVERY AND PRESERVATION

Chapter IV: ISLET ISOLATION AND PRESERVATION

Chapter V: PANCREAS TRANSPLANTATION

Chapter VI: ISLET TRANSPLANTATION

Chapter VII: MANAGEMENT OF PANCREAS GRAFT REJECTION

Chapter VIII: PREVENTION OF ISLET GRAFT REJECTION

Chapter IX: EVALUATION BEFORE AND AFTER TRANSPLANTATION

Experience with prolamine for duct obliteration

W.-D. ILLNER, D. ABENDROTH, R. LANDGRAF, M. GOKEL and W. LAND

Introduction

Clinical transplantation of the pancreas seems to be a promising approach to influence the late diabetic syndrome. This view is corroborated by our recent findings in regard to the development of diabetic eye disease, polyneuropathy and peripheral microcirculation in our pancreatic transplant recipients [1,85]. Mainly due to increasing experience and partly due to the introduction of cyclosporine for immunosuppression [21], results of clinical pancreas transplantation have markedly improved during the last few years, both in terms of functional graft performance as well as patient survival rates. According to the international Pancreas Transplant Registry, the one-year rates of pancreatic graft function were 20% in the period 1978–1982 and 42% in the period 1983–1986, while the patient survival rates improved from 71% in 1978 to 85% in 1986 [128]. This improvement of results was independent of the surgical technique applied for managing the exocrine system.

In this Selected Issue we report on our experience with clinical pancreas transplantation at the Munich Transplant Center, with special emphasis on the use of prolamine for the abolishment of exocrine secretions.

Principles of prolamine for duct occlusion

The use of an alcoholic amino acid solution ('prolamine') in order to destroy the exocrine pancreatic system, originates from the experimental work in animals by Gebhardt and Stolte [51,52]. They were able to demonstrate that an atrophy of the exocrine tissue occurs within a short time after injection of prolamine into the pancreatic ductal system, while the structure and function of the islets of Langerhans remain completely unchanged and well preserved. The cylindric epithelium of the ductal system is destroyed after injection of the occlusive substance. After 3 or 4 days, the prolamine is being lysed by immigrated leukocytes. At the same time, the epithelium of the duct regenerates and is completely restituted by the eleventh day following injection. Apart from these processes, an interstitial sialo-oedema develops with its maximum on the second to fifth day. It is replaced by connective tissue and results in interstitial fibrosis within about 3 weeks. In the mean time, atrophy of the acini develops along with fibrosis of the exocrine parenchyma. In animal experiments, these events are completed after about 60 days (Table V.9).

Before starting the duct injection itself, the corpus-and-tail segment of the pancreas is separated from the spleen in vitro. The cut surface of the pancreatic parenchyma is sutured with absorbable suture material. In order to avoid contact with prolamine the arterial (coeliac axis) and venous (portal vein) vessels of the pancreatic segment are covered with pads. Then a hypodermic needle (preferably with a large lumen) is inserted in the pancreatic duct and fixed with a ligature. The prolamine is injected under X-ray control, using a hypodermic syringe and room-temperature. We consider the occlusion being complete as soon as the so-called 'over-injection-effect' appears on the X-

TABLE V.9

Characteristics of prolamine

1) Solidifies rapidly in the ductal 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 the endocrine function

ray screen, which implies that the prolamine leaves the ductal system and infiltrates into the parenchyma where small spots become visible (Fig. V.20). This procedure requires about 3–4 ml of prolamine. Finally, the needle is retracted and the pancreatic duct ligated.

Patients and methods

The first transplantation of the pancreas at our institution was performed in 1979 [82,84]. Since then, 70 pancreas transplants have been performed. Simultaneous transplantation of pancreas and kidney was carried out in 62 patients with type 1 diabetes. Two patients had to be retransplanted, and six non-uremic diabetic patients received only a pancreas transplant (Table V.10).

Fig. V.20. Procedure of duct injection with prolamine. The duct injection is considered to be efficient when first signs of over-injection appear by X-ray.

TABLE V.10

Pancreas transplantation with duct occlusion in type 1 diabetes*

	No. of patients	No. of pancreas transplants
Pancreas plus kidney	62	62
1979 – 1981	3	
1981 – August 1984	31	
September 1984 – March 1987	28	
Pancreas alone	6	6
Pancreatic retransplantation		2
Total	68	70

*Transplant Center Munich, March 1987.

In all cases, transplantation of a duct-occluded segment of the pancreas was performed, and prolamine (Ethibloc®) was used for duct occlusion. Initially, the graft was placed partly extra- and partly intra-abdominally, as described by Dubernard et al. [41]. As of the end of 1984, the graft was placed strictly intra-abdominally along the colon ascendens, with a short (3 days) period of subsequent postoperative abdominal lavage. Furthermore, our immunosuppressive and anticoagulative regimens were adapted in 1984, in order to guarantee a high immunosuppressive index and to avoid the early irreversible thrombosis of the splenic vein (Table V.11).

TABLE V.11

The present regimen of pancreatic transplantation*

Surgical technique:	Graft completely intraperitoneal Continuous irrigation (3 days)
Immunosuppression:	Quadruple drug induction therapy Triple drug therapy for 6 months Maintenance therapy with cyclosporine and azathioprine
Anticoagulation:	Rheomacrodex® Low dose heparin

*Started in September 1984.

Graft and patient survival rates

It appears justified to present our results of combined pancreas and kidney transplantation by time era, in analogy to the reports from the international Pancreas Transplant Registry [128]. These results are graphically illustrated in Fig. V.21 and V.22.

The results of transplants performed during the period from 1981 until August 1984 were as follows. The pancreatic function rate was 40% (30 months post-transplant) and the renal function rate was 36% (39 months post-transplant) after simultaneous pancreas and kidney transplantation. The corresponding patient survival rate was 83%.

The results of transplants performed during the subsequent period from September 1984 until March 1987 had conspicuously improved. The 30-month function rate was 74% for the pancreas transplants and 71% for the kidney transplants. The patient survival rate was 93%. During this latter period we lost only one patient; this was a 54-year-old male who died with a functioning kidney

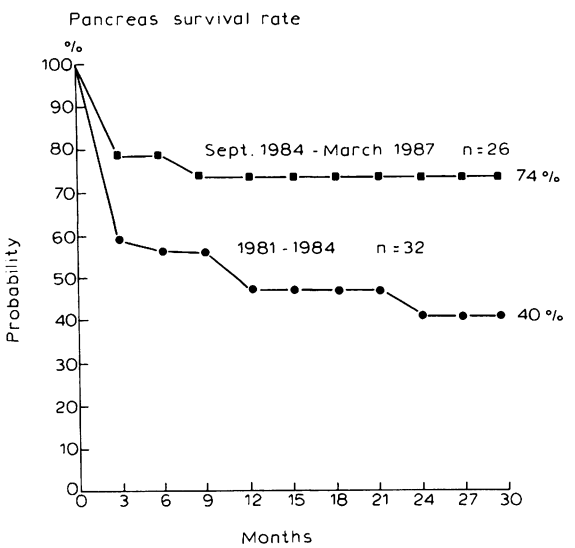

Fig. V.21. Pancreas survival rate in simultaneous pancreas and kidney transplantation according to different periods, using some modifications since September 1984 (Cutler-Ederer formula).

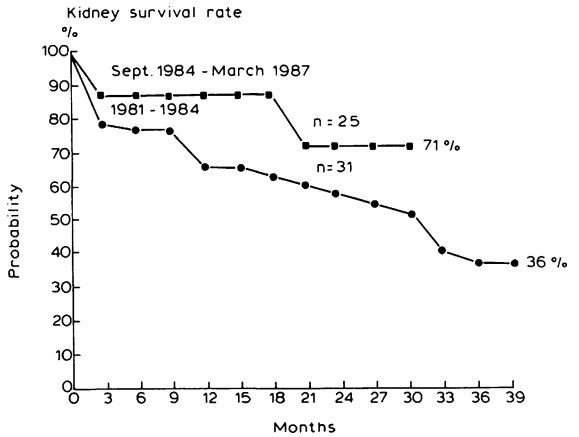

Fig. V.22. Kidney graft survival rate in combined pancreas and renal allotransplantation according to different periods (Cutler-Ederer formula). Since September 1984 some modifications were used.

9 months after simultaneous grafting. In this patient, death was caused by diabetic complications and not by the transplantation itself.

Complications with prolamine

In contrast to the experimental findings in animals [51,52], we have noted a delayed destruction and atrophy of the exocrine parenchyma with histological examination of our clinical material (Fig. V.23). This explains our observation, that about 50% of the prolamine-occluded segmental grafts maintain a marked residual exocrine function and develop a cutaneous pancreatic fistula [74]. This residual exocrine function with fistulation may last during varying periods of time from 8 weeks as a minimum to up to 8 months. The additional medicamentous blocking of the exocrine function with somatostatin appears to influence only the intensity but not the duration of the residual exocrine function. The chance of secondary bacterial infection increases with longer duration of exocrine fistulation, and we call such secondarily infected fistulae 'complicated pancreatic fistula'. Their proper treatment presents a heavy challenge to the surgeon, since not only the function of the graft but also the life of the recipient may depend upon the

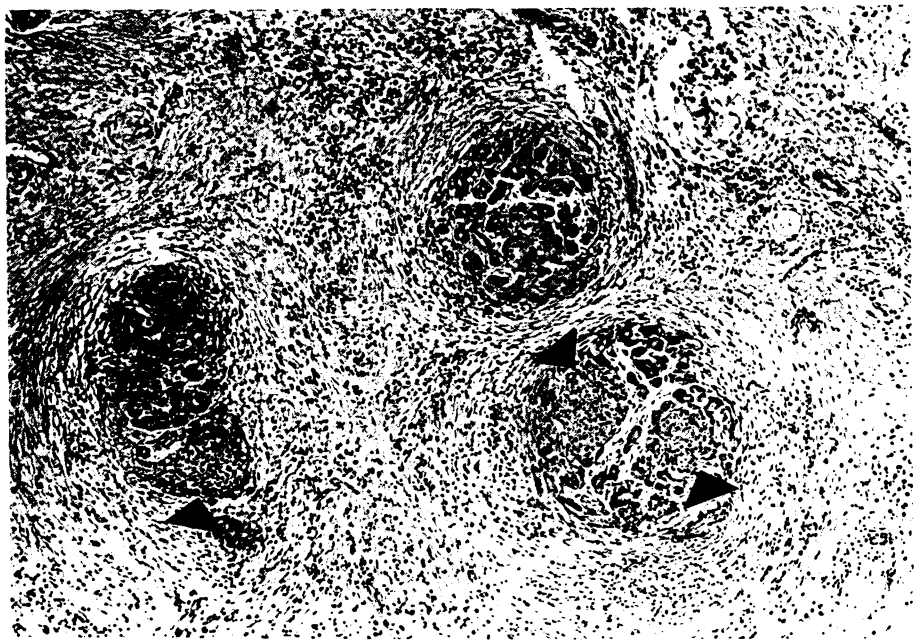

Fig. V.23. Pancreas transplantation: extensive cirrhotic destruction of the exocrine parenchyma due to duct occlusion (day 51 after transplantation). Pancreatic islets well preserved (arrows) (H&E, magnification 50×).

outcome of treatment. As shown in Table V.12, the incidence of pancreatic fistulae was not reduced by placing the pancreatic transplant completely intra-abdominally instead of partly intra- and partly extra-abdominally. Therefore, we now apply a short time (about 3 days) continuous lavage of the abdomen in order to remove the highly active amylase/lipase secretions (which are especially active in the early post-transplant phase). This procedure has been elected in order to: 1) prevent adhesions, and 2) minimize the intra-abdominal volume of these secretions, which probably serve as an ideal 'culture medium' for bacteriae. This modified surgical technique appears to reduce the incidence of local complications caused by complicated pancreatic fistulae and, consequently, to reduce the incidence of pancreatic graft loss (Table V.13). The question why every other recipient of a prolamine-occluded segmental pancreas graft maintains residual exocrine function during varying periods of time remains unanswered and will be the subject of further studies.

TABLE V.12

Incidence of pancreatic fistula using prolamine

Time era	No. of grafts	Incidence of fistulae	
		No.	%
1979 – August 1984	25	13	52
September 1984– March 1987	26	12	46

TABLE V.13

Graft loss due to complicated pancreatic fistulae

Time era	No. of grafts	Graft loss	
		No.	%
1979 – August 1984	25	5	20
September 1984 – March 1987	26	2	8

Metabolic investigations

All of the successfully transplanted patients have normal HbA1 levels and are independent of insulin. Normal oral glucose tolerance tests (as judged by the WHO-criteria) were found in 63% of the cases, but 37% had impaired utilization of glucose. Both in recipients with normal as well as in those with impaired oral glucose tolerance, basal insulin, C-peptide and glucagon levels are somewhat higher than in normal controls. Only patients with an impaired glucose tolerance show a delay in glucose-provoked insulin response and in C-peptide response after arginine stimulation. However, glucagon values after arginine stimulation are similar in patients with either normal or impaired glucose tolerance. One of the most important observations with regard to the technique of duct occlusion is that no deterioration of endocrine graft function was found to occur with time. The mean values of blood glucose levels and insulin responses after glucose loading and arginine stimulation are similar at 4 and 27 months post-transplant. As shown in Fig. V.24, we even found some indication (although not statistically significant) for improvement of endocrine graft performance with time.

These data clearly demonstrate that, at present, we have no reason to suspect a deleterious influence of duct occlusion with prolamine on the endocrine function of segmental pancreatic grafts. Our clinical findings are corroborated by the previous experimental studies of Gebhardt et al. [51,52] and Land et al. [82].

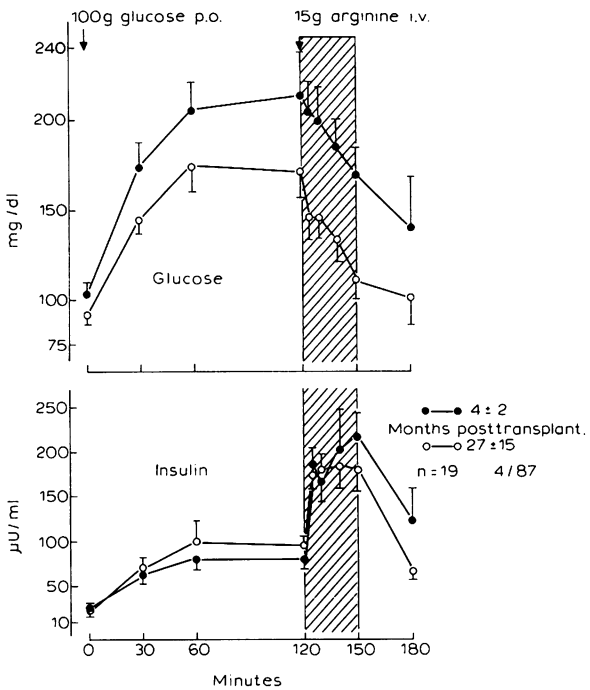

Fig. V.24. Behavior of blood glucose and serum insulin during oral glucose load and i.v. arginine stimulation (▨) according to different periods post-transplant in recipients of simultaneously transplanted pancreas and kidney grafts.

Concluding remarks

The results of simultaneous transplantation of the pancreas and the kidney using the duct-occlusion technique with prolamine have been improved by modifications of: 1) the surgical technique; 2) the immunosuppressive regimen; and 3) the method of anticoagulant prophylactic medication. Seven years of experience with prolamine for duct occlusion have shown that the endocrine function of duct-occluded segmental pancreatic allografts remains unchanged with time. Neither histologic nor metabolic examinations could support the suggestion that fibrosis of the exocrine parenchyma may contribute substantially to eventual endocrine graft failure. The questions why about 50% of the duct-occluded grafts maintain a transient residual function of the exocrine system, and why 63% of the patients have a normal oral glucose tolerance while 37% have not, remain unanswered at the present time.

It should be emphasized that segmental transplantation of the pancreas using duct occlusion with prolamine leads to: 1) a drastic decrease in mortality: 2) acceptable morbidity; 3) a relatively high

rate of adequate graft function; 4) a high rate of psycho-social rehabilitation; and 5) a marked prevention of late diabetic syndromes.

The results of long-term studies will have to be awaited in order to decide upon the question if it is possible to obtain long-lasting prevention of late complications of diabetes by means of successful pancreatic transplantation.