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The bladder drainage technique in pancreas transplantation – the Tübingen experience

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Summary. Starting in 1987 renal- and pancreaticoduodenal - transplantations were performed simultaneously in a consecutive series of 40 patients with Type 1 diabetes mellitus and end-stage renal disease. Exocrine secretion of the pancreatic graft does not seem to be a crucial problem anymore when using the bladder drainage technique. No pancreatic fistulae were seen. No graft lost its function due to early post-operative graft thrombosis. Early post-operative graft pancreatitis and recurrent urinary tract infections remain the drawbacks of the bladder drainage technique. Despite a strong immunestimulation of the recipient by the combined pancreaticoduodenal/ renal allograft all but two rejection episodes could be reversed by using different monoclonal/ polyclonal antibodies. Actuarial 1-year-graft survival rate reaches 85 % for the pancreas as well as the kidney. Thus, simultaneous pancreas-kidney transplantation can be performed with a high success rate when using the technique described.

Key words: Pancreas transplantation - Bladder drainage technique - Immunosuppression - Complications - Graft function rate

Introduction

Exogeneous insulin administration even in its most advanced forms is not able to normalise glucose metabolism adequately. Long-term complete euglycaemia can only be achieved at present by transplantation of insulin producing tissue. Since in the human setting islet transplantation is still in an experimental stage (Hering et al. 1988) pancreatic transplantation remains as the only treatment modality to cure diabetes. Until recently, however, the results of pancreatic transplantation were clearly inferior to those of other solid organ transplantations (Sutherland et al. 1991). Local complications due to the exocrine secretion of the graft, the high incidence of graft thrombosis and the strong immunostimulatory properties of the pancreatic grafts were most crucial in this respect. The introduction of the bladder drainage technique and the use of new immunosuppressive drugs such as cyclosporine A and monoclonal anti T-cell antibodies have solved many of these problems. Using this new approach the transplant centre at the University of Tübingen started in 1987 to treat Type 1 diabetic patients with end-stage renal disease not only with an allogeneic kidney graft but also with a pancreaticoduodenal allograft. The bladder drainage technique was used. The following report describes our experiences with a consecutive series of 40 patients.

Subjects and methods

Patients. Between January 1987 and December 1990 40 Type 1 diabetic patients with end-stage renal disease underwent simultaneous pancreas - kidney transplantation at the University of Tübingen. There were 21 men and 19 women with an age ranging from 26 to 53 years (mean: 39.5 years). The duration of insulin- dependent diabetes was a mean of 24.5 years (11-34 years), the duration of dialysis was 1.9 years (0 - 10.5 years). All recipients had severe extrarenal diabetic complications. Advanced diabetic retinopathy was present in all patients, two were totally blind. Three quarters of the patients suffered from moderate to severe neuropathy and peripheral microangiopathy.

Donor Organs. Kidney and pancreas allografts were harvested from the same cadaveric donors. In 25 of the donors other organs as heart, lung and liver were also removed. Organ perfusion was performed in the first 13 donors with Eurocollins and in the remaining donors with UW solution, with preservation times ranging from 2.5 to 16 h.

Recipient Operation. After graft splenectomy and creation of a blind duodenal segment (Nghiem et al. 1987), all pancreatic grafts were placed intraperitoneally and connected to the right iliac vessels, all kidney grafts were placed extraperitoneally on the left side and connected to the left iliac vessels. A typical side-side anastomosis was performed between the duodenal segment of the pancreatic allograft and the urinary bladder of the recipient.

In all patients a closed continuous abdominal lavage was performed starting 6 to 24 h after the end of operation. A modified peritoneal dialysis machine (Dialyse Technik, Rheinstetten, FRG) as well as modified peritoneal dialysis solutions (Schiwa, Glandorf, FRG) were used. The lavage was performed until disappearance of clinical abdominal symptoms as well as normalisation of leucocyte count and enzyme levels in the lavage fluid.

Anticoagulation. All patients recieved low molecular weight dextran for 5 days (250 ml/24 h) and i.v. heparin for 10 days (PTT > 40 < 50). Antithrombin-III was given whenever antithrombin-III levels in serum fell below 70 %. Beginning at day 10 aspirin was given orally (250 mg every second day).

Immunosuppression. Immunosuppression was started with triple drug therapy. Azathioprine and cyclosporine A were adjusted according to the peripheral leucocyte count (> 3000/µl) and serum level (200 - 250 ng/ml), respectively. Prednisolone was tapered from 100 mg/day to 30 mg/day within 14 days. The last 16 patients received, in addition, prophylactically antithymocyte globulin (ATG, Fresenius, Bad Homburg, FRG) for 10 days. Rejection episodes were treated with corticoid bolus therapy, antithymocyte or antilymphocyte globulin (Pressimun, Behring, Marburg, FRG) or OKT-III (Orthoclone, Cilag, Sulzbach, FRG).

Results

All 40 pancreaticoduodenal grafts showed primary function, 37 of the patients no longer required insulin therapy after reperfusion of the pancreatic graft while three patients had to be treated in the early post-operative period with different amounts of exogeneous insulin in order to achieve normoglycaemia.

In all patients high amounts of amylase could be detected in the abdominal lavage fluid. Amylase concentration reached up to 20,000 IE/l. This high enzyme concentrations in the lavage fluid disappeared in 20 patients within 3 days and in 16 patients within 1 week. Only four patients suffered from prolonged enzyme leakage from the graft for up to 4 weeks due to acute necrotizing graft pancreatitis.

In 28 of the 40 grafts the macroscopic appearance of the pancreatic tissue was essentially normal within the first few hours after reperfusion of the graft. Edemateous graft pancreatitis developed in ten patients. In six patients a more or less severe acute necrotizing graft pancreatitis was seen. In the first of these six patients the graft was removed while in the following five patients the necrotizing graft pancreatitis could be treated successfully by repeated local necrectomies and a prolonged closed continuous peritoneal lavage. In all of these grafts exocrine function declined or disappeared completely while endocrine function was preserved.

Early post-operative graft thrombosis was not seen in this series. Six of the patients had to be reoperated because of local active bleeding or for evacuation of a local haematoma.

More than 75 % of patients suffered from rejection episodes. The highest frequency of rejections was seen within the first 3 postoperative months. Later rejection episodes were rare. All rejection episodes regarding the pancreas graft could be reversed successfully, two kidney grafts lost their function due to irreversible rejection.

At the moment 35 of the 40 patients are still alive. two died within the first 3 post-operative months from pyelonephritis within their own kidneys and from virus-myocarditis, respectively. The other three patients died late after transplantation from a pulmonary embolus, a systemic infection with anaerobic germs and from a progressive micro- and macroangiopathy with disseminated necroses at all four extremities and the trunk, respectively. In all of these three patients the pancreatic allograft was still functioning at the time of death, while in two of them the kidney graft function was lost several months earlier due to rejection.

Actuarial 1-year graft survival is 85 % for the pancreas as well as the kidney graft (Fig. 1) . The mean creatinine after 1 year levels at 1.6 mg%. All of the patients are insulin-independent and normoglycaemic with HbA1 values within the normal range. Actuarial 3-year graft survival of the pancreas remains at 85 % while kidney graft survival rate is reduced to 75 %.

More than 90 % of the recipients with functioning grafts have experienced an immense improvement in general well-being and quality of life according to their own judgement.

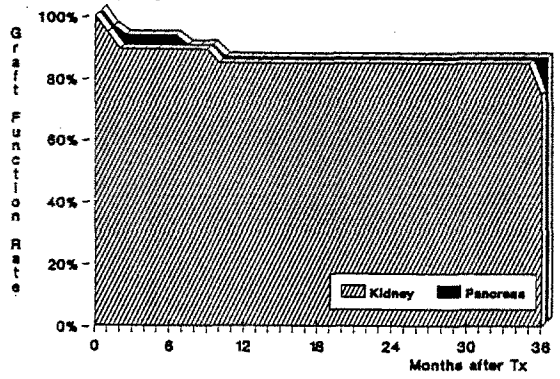

Fig.1: Actuarial function rate of the pancreas and kidney allograft after pancreaticoduodenal/renal transplantation in Type 1 diabetic patients with end-stage renal disease.

Discussion

Pancreatic transplantation is, at the moment, the only treatment modality which is able to definitely cure Type 1 diabetes (Östman et al. 1989). The success rate of pancreatic transplantation, however, has lagged behind the other solid organ grafts mainly for two reasons. First of all high technical failure rates of up to 30 % were reported (Prieto et al. 1987, Sutherland et al. 1991). As shown in this series, however, the technical failure rate can now be dramatically reduced when using the technique described. The bladder drainage technique warrants an absolutely safe management of the exocrine secretions of the graft (D'Alessandro et al. 1989). Contrary to the duct occlusion technique (Abendroth et al. 1989), no long lasting pancreatic fistulae with secondary deep wound infections were seen. The problems with graft pancreatitis which are peculiar for whole organ grafts with free drainage into the gut or the bladder can be managed when using the therapeutic regimen described by us. In our opinion closed continuous peritoneal lavage is not only an excellent tool for treating graft pancreatitis but also for prevention and treatment of intraabdominal infections.

None of our pancreatic grafts lost their function due to graft thrombosis. This is in sharp contrast to the reports in the literature, where a thrombosis rate of 10 % - 20 % is common (Sutherland et al. 1989; Martin et al. 1990; Sutherland et al. 1991). A meticulous operative technique as well as adequate anticoagulation therapy might be responsible for the complete lack of post-operative thrombosis in this series. Despite the moderately increased post-operative bleedings we still believe that anticoagulation therapy should be used after pancreatic transplantation.

The incidence of early rejections in combined pancreas-kidney transplanted patients is 2 to 3 times as high as for example in patients with isolated kidney grafts (Hopt et al. 1989). Nevertheless, when using quadruple immunosuppressive therapy as initial treatment and monoclonal as well as polyclonal antibodies for treatment of rejection episodes graft function loss due to immunological reasons is low (Sollinger et al. 1988). All patients were immunologically stable after 3 months. The frequency of rejection episodes in the later phase was very low and did not differ from that of patients with isolated kidney grafts.

Patient survival in our series was similar to that reported from the world registry (Sutherland et al. 1991). Nevertheless, it should be improved. Considering the late deaths most of them are directely related to preexistent secondary diabetic lesions. When excluding, however, all patients with severe secondary diabetic lesions from pancreatic transplantation, one will exclude just those patients who - at least in our experience - might gain most regarding their well-being and quality of life.

One-year-graft function rate in our series for the pancreas and kidney graft certainly is excellent. It demonstrates that in specialized centres graft function rate after pancreaticoduodenal/renal transplantation equals now for the first time that after isolated kidney transplantation (Sollinger et al. 1988; Cosimi et al. 1988). Even after 3 years actuarial graft function rate is extremely high for the pancreas as well as for the kidney graft. Considering the enormous gain in general well-being and quality of life (Nakache et al. 1989; Corry et al. 1990) simultaneous pancreas kidney transplantation in the described technique can be recommended as an approved and very successful therapy for Type 1 diabetic patients with end-stage renal disease.

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