

Pancreaticoduodenal transplantation with portal venous and enteric drainage in rats

Yong Ping Gu¹, Jian Yun Gu² and Jie Shou Li¹

Subject headings pancreaticoduodenal transplantation; kidney transplantation; portal venous drainage; enteric drainage; postoperative complications; rats

Gu YP, Gu JY, Li JS. Pancreaticoduodenal transplantation with portal venous and enteric drainage in rats. *World J Gastroentero*, 2000;6(6): 914-916

INTRODUCTION

The use of combined pancreatic and renal transplantation in patients with diabetes and end-stage renal failure has gained widespread recognition as an acceptable treatment option. The prevailing method used for transplantation of the pancreas involves anastomosis of the graft's portal vein and the recipient's iliac vein to provide systemic venous drainage of the graft, and a duodenocystostomy to provide bladder drainage of exocrine secretions^[1]. Although graft survival rates have improved with the use of this technique, potential postoperative problems arise due to the physiologically abnormal exocrine and venous drainage of the pancreas allograft. Bladder drainage of exocrine secretions increased the loss of bicarbonate in the urine, creates electrolyte derangements, and contributes to dehydration leading to a state of metabolic acidosis^[2-4]. Pancreatic secretions drained into the bladder also provide a constant source of irritation to the bladder mucosa, accentuating the abnormalities associated with autonomic diabetic dysfunction. This environment subsequently led to recurrent hematuria, infection, and repeated episodes of graft pancreatitis^[5-7]. The method of pancreas transplantation with portal venous and enteric drainage can overcome these problems. One of the earliest series of portal pancreatic transplants was reported in 1984^[8]. Because of the complex surgical technique, big animal models were used widely in the pancreas transplantation research^[9-11], up to now, there has been only portal venous drainage in

segmental pancreatic transplantation in rats^[12]. In our study, we established an animal model of pancreaticoduodenal transplantation with portal venous drainage through the superior mesenteric vein and enteric drainage in rats in order to achieve a better understanding of the immunology and physiology of this graft.

METHODS

Inbred male Wistar rats (220g-330g body weight) were used as the recipients and the donors, the recipient weight was 50g higher or so than the donor. At the beginning, all recipients were measured for blood insulin concentrations using radioimmunoassay as previously described^[13], diabetes was induced by a single intravenous injection of streptozocin (Sigma Chemical Co, St. Louis, MO) at a dose of 55mg/kg. Rats with nonfasting plasma glucose levels of more than 22mmol/dL were used as recipients.

The donors received 5% glucose and 0.9% saline for 24 hours and the recipients received 2.5% glucose and 0.45% saline for 24 hours before surgery. They were anesthetized with an intraperitoneal injection of pentobarbital (40mg/kg) and chloral hydrate (160mg/kg i.p.) supplemented with the pentobarbital as required.

We used a modified method reported by Lee and Li^[14,15], to minimize graft trauma. Pancreaticoduodenum was harvested from the donor rats with an attached segment of donor's aorta including the superior mesenteric artery and celiac truncus as arterial inflow and the portal vein was maintained for venous outflow, and the proximal end of duodenum was ligated with 3-0 silk and the 2cm of distal duodenum was removed. The spleen arteries and veins were ligated with 5-0 silk, but did not remove the spleen. The graft was flushed with 2mL-3mL cold heparinized lactated Ringer's solution (25U/mL), removed, and stored in cold lactated Ringer's solution (4°C) until transplantation into the recipient rat. Finally, 2.5mL-3mL fresh blood was taken from the donor's abdominal aorta with 5U heparin.

All the recipients were given 8mL-12mL of 0.9% saline by subcutaneous injection and were opened via a middle incision. Segments of the recipient abdominal aorta were mobilized below the vessels to the left kidney. A modified Lee's clamp^[16] was placed across the aorta. The aorta was punctured with a 30 gauge needle and opened via a longitudinal arteriotomy. The lumen was flushed

¹Transplantation Center, Nanjing General Hospital, Nanjing University School of Medicine, Nanjing, China

²Unit of Chemical Analyses, Jiangsu Pharmaceutical Company
Yong Ping Gu, graduated from Nanjing Medical University in 1990, majoring in pancreas transplantation, having 8 papers published.

This work was supported by a grant from the Army Medical Science and Technology Research, No.96Z002

Correspondence to: Yong Ping Gu, M.D., Ph.D. Candidate. Transplantation Center, Nanjing General Hospital, Nanjing 210002, Jiangsu Province, China

Email: guyongping@yahoo.com

Received 2000-06-13 Accepted 2000-06-29

with heparinized lactated Ringer's solution. The superior mesenteric vein was isolated at a low level. The superior mesenteric vein was controlled proximally with a microvascular clamp and was ligated distally with 5-0 silk and the superior mesenteric artery was ligated at the same level and manner. The superior mesenteric vein was cut off between the microvascular clamp and silk ligation point as closely as possible to the latter, and the lumen was flushed with heparinized lactated Ringer's solution. The ischemia small intestine (about 30%-40%) and ileocecum were removed, an end-to-end intestinal anastomosis was performed using one layer of full thickness 7-0 nylon suture. The donor graft was removed from the ice water and wrapped by a wet gauze sponge packed with ice crystals.

The venous anastomosis was made first. After ensuring that the vein was not twisted, an end-to-end anastomosis of the donor portal vein and the recipient superior mesenteric vein was made using 10-0 nylon interrupted suture. The vein was irrigated with saline to keep the vessel walls apart during the venous anastomosis and gently teased apart before tying the sutures to avoid stricture of this anastomosis. Next, an end-to-side arterial anastomosis of the donor arterial segment and the recipient abdominal aorta was performed using continuous 9-0 nylon suture. The venous clamp was released first, followed by the arterial clamp. The arterial anastomosis was compressed lightly with a dry sponge for 1-2 minutes after reperfusion. Finally, we performed an end-to-side intestinal anastomosis of the donor distal end duodenum and the recipient jejunal side and removed the donor spleen.

Twenty milliliters of warm saline was instilled in the peritoneal cavity prior to closing the abdomen, 2.5mL-3mL donor blood was injected via the dorsal penile vein as the final procedure.

The time for the donor surgery was about 45 minutes, and for the recipient surgery was 90 minutes, the vein anastomosis was 25 minutes and the arterial anastomosis 15 minutes.

The rats were kept on a warming blanket and under a heating lamp for the first 24 hours. They usually recovered from the anesthesia within 1 hour after the operation. They were given 30mL-40mL of 2.5% glucose and 0.45% saline daily containing 150mg piperacillin sodium by subcutaneous injections for the 36-48 hours, followed by normal diet accordingly.

RESULTS

We finished 67 cases of consecutive pancreatic transplantations with portal vein drainage through superior mesenteric vein and enteric drainage. Forty-six rats survived over 7 days, the success rate was 68.6%(46/67). The most common causes of postoperative deaths within the first few hours were

venous thromboses in the anastomosis (18.9%, 12/67). Eight deaths occurred due to hypovolemic shocks within the first 48 hours, one death due to enteric leakage. Rats that survived over 48 hours generally could survive indefinitely. The nonfasting plasma glucose levels of successful rats (91.3%, 42/46) were turned normal. Though the other four cases were still hyperglycosemia, the plasma glucose levels became significantly lower than the preoperative value. All successful 46 cases were measured for insulin concentrations again, the values did not change significantly.

DISCUSSION

Most patients with a systemically draining pancreatic graft displayed both hyperinsulinemia and insulin resistance, sensitivity and responsiveness to insulin in removing glucose decreased^[17]. In this model of pancreas allograft using venous drainage into portal vein and enteric drainage rather than systemic vein and bladder exocrine drainage, it is more closely approximated to enteric drainage and venous drainage of the pancreas allograft in physiology and to avoid the impairment of the first-pass removal of insulin by the liver, otherwise it leads to hyperinsulinemia and insulin resistance^[7,17,18]. Meanwhile, we chose the venous anastomoses at lower level of superior mesenteric vein without heparinizing the recipient rather than the portal vein in order to avoid the venous thromboses at high level and prevent the whole intestinal injury. Once the venous thrombosis happened, the graft could be removed without impairment of the recipient intestine, and the manipulation was rather easy.

The venous thromboses were the most common causes of postoperative deaths, the high blood flow through superior mesenteric vein and the technique of venous anastomosis were responsible for the venous thromboses. To overcome high blood flow through superior mesenteric vein, we took the following measures: ① the recipient was 50g heavier than the donor; ② remove 2cm of donor's distal duodenum; ③ ligate the donor spleen arteries and veins at operation. The end-to-end anastomosis of the donor portal vein and the recipient mesenteric vein was likely to be twisted and narrowed, we therefore, performed the venous anastomosis first and solved these problems readily.

It has been indicated that hypovolemic shock is the most common cause of deaths occurring immediately after transplantation in the small animal. Continuous rat intravenous infusion of the tail vein and the dorsal penile vein, were adopted by many colleagues^[19]. But we gave the recipient 8mL- 12mL of 0.9% saline by subcutaneous injection at the beginning and 2.5mL-3mL fresh blood via the dorsal penile vein as the final procedure^[19], instead of keeping long-time continuous intravenous infusion during the surgical

procedure. The 2.5mL-3mL donor blood could eliminate the most frequent causes hypovolemic shock of postoperative mortality after organ transplantation.

The enteric drainage of exocrine secretion can avoid the loss of bicarbonate in urine, otherwise which will result in eletrolyte derangements and dehydration, leading to a state of metabolic acidosis. These distinct advantages reduced postoperative complications markedly in rats, and provided a better understanding for the immunology and physiology of the pancreaticoduodenal transplantation. These are of important clinical significance.

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Edited by You DY and Ma JY