P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(9):2125-2127
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORTS •

Modifications in combined liver-small bowel transplantation in pigs

Feng Jiang, Zhen-Yu Yin, Xiao-Dong Ni, You-Sheng Li, Ning Li, Jie-Shou Li

Feng Jiang, Zhen-Yu Yin, Xiao-Dong Ni, Medical School of Nanjing University, Nanjing 210093, Jiangsu Province, China
You-Sheng Li, Ning Li, Jie-Shou Li, Research Institute of General Surgery, General Hospital of PLA, Nanjing Military Command, Nanjing 210002, Jiangsu Province, China
Supported by the Military Medical Research Found of China, No. 96M022, and by the Major Project of Nanjing Military Command, No.02Z001
Correspondence to: Dr. Ning Li, Research Institute of General Surgery, General Hospital of PLA, Nanjing Military Command, Nanjing 210002, Jiangsu Province, China. jiangfeng174@sohu.com
Telephone: +86-25-4824804 **Fax:** +86-25-4803956
Received: 2002-12-28 **Accepted:** 2003-02-11

Abstract

AIM: To introduce combined liver-small bowel transplantation in pigs.

METHODS: Eighteen transplantations in 36 large white pigs were performed. Three modifications in combined liver-small bowel transplantation model were applied: Veno-venous bypass was not used. Preservation of the donor duodenum and head of pancreas in continuity with the combined graft to avoid biliary reconstruction. The splenic vein of donor was anastomosed end-to-end with the portal vein of recipients by the formation of a "cuff".

RESULTS: Without immunosuppressive therapy, 72-hour survival rate of the transplanted animals was 72 % (13/18). Five of 18 pigs operated died of respiratory failure (3 cases) and bleeding during hepatectomy (2 cases). The longest survival time of animals was 6 days.

CONCLUSION: Our surgical modifications are feasible and reliable, which have made the transplantation in pigs simpler and less aggressive, and thus these can be used for preclinical study.

Jiang F, Yin ZY, Ni XD, Li YS, Li N, Li JS. Modifications in combined liver-small bowel transplantation in pigs. *World J Gastroenterol* 2003; 9(9): 2125-2127
http://www.wjgnet.com/1007-9327/9/2125.asp

INTRODUCTION

Despite intestinal transplantation technique for the treatment of irreversible failure of the intestine has been improved, clinical intestinal transplantation still remains at an experimental stage. Compared with other solid organ transplantations, attempts at human small bowel transplantation had disappointed results in terms of survival of patients and grafts[1-4]. Bowel transplant can also be performed as a part of a multivisceral graft[5]. Even though total parenteral nutrition (TPN) and home parenteral nutrition (HPN) allow many patients with intestinal failure to live with a high life quality, it has some severe and even fatal complications, such as catheter sepsis, severe cholestasis, and chronic secondary hepatopathy[6-8]. Many institutions have performed combined liver-small bowel transplantations in human and small animals, but few studies were conducted in large animals[9]. Pigs are one of the standard models for large animal transplantation due to the anatomic features. In order to improve clinical prognosis of liver-small bowel transplantation (LSBT), we investigated the modifications of the experimental model.

MATERIALS AND METHODS

Large white pigs weighing 25±5 kg were used for LSBT under general anesthesia[10]. Animals were fasted with free access to water for 24 hours prior to surgery. The size of donor pigs was the same as or smaller than that of recipients.

Donor operation

After vascular cannulation for venous and hemodynamic monitoring, the abdomen was entered at middle line xipho-pubic incision. After transection of transverse colon, the whole intestine tract was inspected thoroughly. Total colon including the ileocecal valve was transectioned. Hepato-gastric and spleno-gastric ligaments including splenic and left gastric arteries were ligated. The splenic vein was prepared for perfusion, and the ligaments around the liver were mobilized. Then the abdominal aorta was dissected from infrarenal aorta until one centimeter cranially to celiac axis. Lymphatic vessels were tied carefully to avoid lymphorrea after transplantation. And the vena cava was also dissected from infrarenal until suprahepatic cava. Before systemic heparinization, blood was drawn and saved for use in recipient operations. Before clamping the cranial aorta upper the celiac axis, the distal aorta was cannulated and 1.5 liter of UW solution was perfused through the infrarenal aorta and splenic venous *in situ* and venting from the supra diaphragm vena cava and infrarenal vena cava. To ameliorate cooling of the graft, the abdominal cavity was filled with cold saline and melting ice. Then the liver-small bowel was *en bloc* harvested in continuity with duodenum and pancreas.

Bench surgery

The *en block* liver-small bowel was preserved in cold UW solution with melting ice. The proximal aorta and the thoracic vena cava were ligated. The vascular pedicles for vascular anastomoses were prepared. Diaphragm veins were ligated and a continuous hemostatic suture was performed. The subtotal pancreas was transected, leaving the head and uncinate processing attached to the duodenum. The stump of the pancreas was stapled and then over-sewn with a continuous suture using 0/4 polypropylene.

Recipient operation

During the recipient operation, the end-tidal carbon dioxide, electrocardiogram and arterial, central vein, and pulmonary artery pressure were monitored.

The abdomen was accessed at a middle line xipho-pubic incision. Firstly a cystostomy was performed using a Foley's

catheter. The small bowel was resectioned except for short segments of proximal jejunum and distal ileum. The recipient' s infrarenal aorta and the vena cava were dissected and encircled for anastomosis. The hepatic hilum was transected with the portal vein preserved. Then hepatectomy was performed with preservation of hepatic part encircling the vena cava. In this period, transfusion was necessary. Three vascular anastomoses between the recipient and the donor were performed as followings: The recipient' s infrarenal vena cava side-to-end anastomosis with donor' s infrahepatic vena cava with continuous 4/0 polypropylene suture, the recipient' s infrarenal aorta side-to-end anastomosis with the donor' s infrarenal aorta with continuous 4/0 polypropylene suture, and the recipient' s distal portal vein end-to-end anastomosis with donor' s splenic vein by the formation of a "cuff". The gut continuity was established proximally between allograft jejunum and native jejunum and distally between allograft ileum and native ileum. A loop enterostomy was performed for endoscopies after transplantation. At last, a gastrostomy was performed to reduce the gastric pressure.

RESULTS

Mean operation time in the donor and recipient was 3.5 hours±10 minutes and 4.5 hours±15 minutes, respectively. During the recipient operation, there was no obvious hemodynamic alteration. Survival rate at 72 hours was 72 % (13/18). Three pigs died of respiratory failure and two of bleeding during hepatectomy. The longest survival time was 6 days without immunosuppression.

DISCUSSION

Multivisceral transplantation was firstly performed for the treatment of short bowel syndrome complicated with liver failure due to long-term hyperalimentation[11]. Starzl reported the first study in dogs in 1960s. Investigations with large animals have shown that multivisceral transplantation is a technically complicated procedure with high mortality[12]. We have been studying on improving surgical techniques of the transplantation for more than 6 months and performed 18 consecutive operations with three innovations.

Firstly, veno-venous bypass, necessary in the conventional experiments[9], was avoided, and thus made the operation simple and less aggressive. It also reduced the incidence of bleeding due to heparinization in operation. Considering the anatomic features of pigs, bleeding in hepatectomy in recipients is unavoidable. But based on our experiences in many preliminary operations, we could control this operative bleeding with the new techniques. In order to keep the recipient hemodynamicaly stable during this period, transfusion and solution were necessary. With this modification the duration of unhepatic period was also shortened.

Secondly, preservation of the donor duodenum and head of pancreas in continuity with the combined graft avoided the need for biliary reconstruction. The standard technique involved an obligatory reconstruction of the biliary system with a defunctionalized loop of proximal allograft jejunum[13]. Consequent limitations of this technique were biliary leaks, obstructions and strictions[14]. In our surgical technique, we eliminated hilar dissection, leaving the hepatoduodenal ligament undisturbed by including the intact duodenum and a rim of pancreatic tissue in the allograft. Apart from obviating biliary anastomotic complications and potential vascular torsion of the small bowel graft[14, 15], surgical modifications also made bench surgery simpler. This modification was applied in human transplantation with satisfaction[14,15]. Debera *et al*[15] reported that the remaining head of the pancreas on the combined liver-small bowel allograft was not associated with a high incidence of pancreatic complications.

The third modification was that the donor splenic vein was end-to-end anastomosed to the recipient' s distal portal vein by the formation of a "cuff". In the standard technique, the recipient' s portal vein was end-to-side anastomosed with the donor portal vein or supra mesenteric vein to avoid portal hypertension in native remnant viscera[9,15,16]. This innovation shortened the operation time, simplified the surgical procedure and also reduced venous stagnation of the allograft and native viscera.

Our technical refinements have made combined liver-small bowel transplantation in pigs simpler and less aggressive. And the technique of this model is feasible and can be used for preclinical study. However, animals experienced with this operation were faced with life threatening respiratory failure, infection, GVHD and rejection[17-27]. Much more work should be done to improve the outcomes of both experimental and clinical combined liver-small bowel transplantations.

REFERENCES

1 **Bramhall SR**, Minford E, Gunson B, Buckels JA. Liver transplantation in the UK. *World J Gastroenterol* 2001; **7**: 602-611
2 **Zhu XF**, Chen GH, He XS, Lu MQ, Wang GD, Cai CJ, Yang Y, Huang JF. Liver transplantation and artificial liver support in fulminant hepatic failure. *World J Gastroenterol* 2001; **7**: 566-568
3 **Grant D**. Intestinal transplantation: 1997 report of the international registry. Intestinal Transplant Registry. *Transplantation* 1999; **67**: 1061-1064
4 **Dionigi P**, Alessiani M, Ferrazi A. Irreversible intestinal failure, nutrition support, and small bowel transplantation. *Nutrition* 2001; **17**: 747-750
5 **Rossi G**, Gatti S, Reggiani P, Galmarini D, Privitera G, Velio P, Melada E, Romito R, Latham L, Vannelli A, Langer M, Codazzi D, Prato P, Fassati LR. Small bowel transplantation under oral immunosuppression: Experimental study in the pig. *Transplant Proc* 1997; **29**: 1816-1818
6 **Schraut WH**. Current status of small-bowel transplantation. *Gastroenterology* 1988; **94**: 525-538
7 **Pritchard TJ**, Kirkman RL. Small bowel transplantation. *World J Surg* 1985; **9**: 860-867
8 **Beath SV**, Needham SJ, Kelly DA, Booth IW, Raafat F, Buick RG, Buckels JA, Mayer AD. Clinical features and prognosis of children assessed for isolated small bowel or combined small bowel and liver transplantation. *J Pediatr Surg* 1997; **32**: 459-461
9 **Gatti S**, Rossi G, Albani AP, Reggiani P, Caccamo L, Gridelli B, Lucianetti A, Paone G, Campanati L, Melada E, Galmarini M, Orsenigo R, Armiraglio E, Andreoni P, Di Mauro P, Reali Forster C, Proietti D, Pifferi S, Doglia M, Fassati LR, Galmarini D. Orthotopic liver-small bowel allotransplantation-surgical technique in the pig. *Transplant Proc* 1994; **26**: 1627-1628
10 **Pirenne J**, Gruessner AC, Benedetti E, Troppmann C, Nakhleh RE, Uckun FM, Gruessner RW. Donor-specific unmodified bone marrow transfusion does not facilitate intestinal engraftment after bowel transplantation in a porcine model. *Surgery* 1997; **121**: 79-88
11 **Zhu Y**, Furukawa H, Nakamura K, Starzl TE, Todo S. Multivisceral allotransplantation in pigs. *Transplant Proc* 1996; **28**: 2725
12 **Mitsuoka S**, Tanaka N, Orita K. Comparison of patterns of rejection in multivisceral transplantation and abdominal organ cluster transplantation in pigs. *Transplant Proc* 1994; **26**: 2450-2454
13 **Grant D**, Wall W, Mimeault R, Zhong R, Ghent C, Garcia B, Stiller C, Duff J. Successful small-bowel/liver transplantation. *Lancet* 1990; **335**: 181-184
14 **Bueno J**, Abu-Elmagd K, Mazariegos G, Madariaga J, Fung J, Reyes J. Composite liver-small bowel allografts with preservation of donor duodenum and hepatic biliary system in children. *J Pediatr Surg* 2000; **35**: 291-296
15 **Sudan DL**, Iyer KR, Deroover A, Chinnakotla S, Fox IJ Jr, Shaw

BW Jr, Langnas AN. A new technique for combined liver/small intestinal transplantation. *Transplantation* 2001; **72**: 1846-1848

16 **Todo S**, Tzakis AG, Abu-Elmagd K, Reyes J, Fung JJ, Casavilla A, Nakamura K, Yagihashi A, Jain A, Murase N, Iwaki Y, Demetris AJ, Thiel DV, Starzl TE. Cadaveric small bowel and small bowel-liver transplantation in humans. *Transplantation* 1992; **53**: 369-376

17 **Gruessner RW**, Nakhleh RE, Harmon JV, Dunning M, Gruessner AC. Donor-specific portal blood transfusion in intestinal transplantation a prospective, preclincal large animal study. *Transplantation* 1998; **66**: 164-169

18 **Perego C**, Marelli O, Rossi G, Gatti S, Reggiani P, Orsenigo R, Galmarini D, Franco P. Orthotopic liver-small bowel transplantation in pigs: study of immunologic parameters during therapy with FK 506-based immunosuppressive regimens. *Transplant Proc* 1996; **28**: 2471-2473

19 **Abu-Elmagd K**, Todo S, Tzakis A, Furukawa H, Nour B, Reyes J, Nakamura K, Scotti-Foglieni C, El-Hammadi H, Kadry Z, Fung J, Demetris J, Starzl TE. Rejection of human intestinal allografts: alone or in combination with the liver. *Transplant Proc* 1994; **26**:1430-1431

20 **Cicalese L**, Sileri P, Asolati M, Rastellini C, Abcarian H, Benedetti E. Infectious complications of following living-related small bowel transplantation in adults. *Transplant Proc* 2001; **33**: 1554-1555

21 **Li YX**, Li JS, Li N. Improved technique of vascular anastomosis for small intestinal transplantation in rats. *World J Gastroenterol* 2000; **6**: 259-262

22 **Farmer DG**, Mc Diarmid SV, Smith C, Stribling R, Seu P, Ament MA, Vargas J, Yersiz H, Markmann JF, Ghobriel RM, Goss JA, Martin P, Busuttil RW. Experience with combined liver-small intestine transplantation at the vniversity of California, Los Angeles. *Transplant Proc* 1998; **30**: 2533-2534

23 **Goulet O**. Intestinal failure in children. *Transplant Proc* 1998; **30**: 2523-2525

24 **Cicalese L**, Sileri P, Green M, Abu-Elmagd K, Kocoshis S, Reyes J. Bacterial translocation in clinical intestinal transplantation. *Transplantation* 2001; **71**: 1414-1417

25 **Li YS**, Li JS, Li N, Jiang ZW, Zhao YZ, Li NY, Liu FN. Evaluation of various solutions for small bowel graft preservation. *World J Gastroenterol* 1998; **4**: 140-143

26 **Todo S**, Tzakis AG, Abu-Elmagd K, Reyes J, Nakamura K, Casavilla A, Selby R, Nour BM, Wright H, Fung JJ, Demetris AJ, Van-Thiel DH, Trarzl TE. Intestinal transplantation in composite visceral grafts or alone. *Ann Surg* 1992; **216**: 223-233

27 **Khan FA**, Kato T, Pinna AD, Berho M, Nery JR, Colombani P, Tzakis AG. Graft failure in two multivisceral transplant recipients secondary to necrotizing enterocolitis. *Transplant Proc* 2000; **32**: 1204-1205

Edited by Ren SY and Wang XL