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Intestinal Transplantation in Children Under FK 506 Immunosuppression

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● **Intestinal transplantation, solitary (n = 3) or in combination with the liver (n = 7), was performed in 10 pediatric patients with intestinal failure. The liver was only replaced if there was liver failure and portal hypertension. Immunosuppression was based on FK 506. Two patients died, one of graft-versus-host disease and one of lymphoproliferative disease. One patient was still in the intensive care unit 1 month posttransplantation due to perioperative complications. The function of the intestinal grafts in the remaining patients is normal. All nutrition and medications including immunosuppression are being administered enterally. This series indicates that small bowel transplantation, alone or in combination with the liver, is feasible in pediatric patients.**

INDEX WORDS: Intestinal transplantation; liver transplantation; FK 506 immunosuppression.

CADAVERIC intestinal transplantation in combination with the liver[1,2] or alone[3,4] is now practical and reproducible[4] and promises to revolutionize the treatment of intestinal failure as liver transplantation did for liver failure more than 10 years ago. Optimism has been moderated mainly by the complexities of the procedure and its postoperative course.

The first example of a functional human intestinal transplant was not achieved until 1987 in a child who underwent multivisceral transplantation under cyclosporine.[5] When this and a second patient died of lymphoproliferative disease, a moratorium on intestinal transplantation was declared at the University of Pittsburgh until FK 506 immunosuppression became available. The pediatric and adult series were developed contemporaneously. The longest surviving child, the recipient of a combined liver-intestinal graft 2 years ago,[6] has enjoyed a normal life style for essentially all of her postoperative life.

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Presented at the 39th Annual International Congress of the British Association of Paediatric Surgeons, Leeds, England, July 15-18, 1992.

Supported in part by research grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, MD.

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0022-3468/93/2808-0019$03.00/0

We are presenting our whole experience with pediatric intestinal transplantation under FK 506 immunosuppression, with emphasis on the unexpected ease with which isolated intestinal transplantation has been accomplished.

MATERIALS AND METHODS

Selection of Recipients

All recipients had intestinal insufficiency and were dependent on total parenteral nutrition (TPN) for survival. Recipients of the combined graft had advanced TPN-induced liver disease and portal hypertension. History of jaundice did not qualify the patients for liver grafting.

Donors

Donors were heart-beating cadavers of identical ABO blood group and similar size. HLA typing was random. Procurement of the organs was part of multiple organ harvesting. Preservation was with the University of Wisconsin solution. The small bowel from the ligament of Treitz to the ileocolic valve was used. No effort was made to ablate the donor's lymphatic tissue, nor was any luminal flushing performed.

Principles of Recipient Procedure

All of the intraabdominal transplant procedures involving more than one organ are variations of an experimental procedure called multivisceral transplantation.[7] Arterialization of the grafts was by anastomosis to the infrarenal aorta. The outflow of the solitary intestinal grafts was into the recipient portal system, either by anastomosis to the native superior mesenteric vein or, in cases with previous abdominal operations, by placing the graft piggy back onto the extrahepatic portal vein by means of end to side anastomosis.[8]

In combined liver-intestinal grafts the outflow was through the hepatic veins and into the inferior vena cava. The native portal vein was drained into the donor portal vein except patient 1, in whom it was drained into the inferior vena cava.

Intestinal continuity was established (except in patient 4, who had an atretic rectum) by anastomosing the proximal end of the donor gut to the recipient's upper gastrointestinal tract. The distal end of the donor gut was brought out on the abdominal wall as an ileostomy. The proximal end of the recipient's colon was anastomosed end to side to the donor distal ileum.

A feeding jejunostomy was performed in the last 3 cases. If a gastrosotmy preexisted, it was left intact (n = 2).

Monitoring of Rejection

Monitoring of rejection for the liver was as in liver transplantation. For the intestine, mucosal biopsies were performed with a cup forceps near the stoma or with endoscopy. Multiple samples were obtained twice per week for a month, then at decreasing frequency and when clinically indicated.

Prevention of Rejection

Prevention of rejection was based on FK 506 and steroids. All patients were started on the same dose of FK 506 (0.15 mg/kg/d) intravenously at the time of transplantation as a continuous infusion. When enteral feedings were tolerated FK 506 was given enterally at 0.3 mg/kg/d in 2 divided doses. The dose of FK 506 was reduced in the face of deteriorating renal function and was increased in the face of rejection. Blood levels were obtained daily at first, then at decreasing frequency. The desirable blood level was thought to be 1 to 3 ng/mL.

The steroid dose was different in the two groups. A bolus of hydrocortisone (1,000 mg) was given intraoperatively in the cases of solitary intestinal transplantation, followed by methylprednisolone (100 mg/d) tapered to baseline within 5 days. The recipients of combined grafts received only the baseline dose which was common to the 2 groups: 20 mg/d for patients over 10 kg of body weight and 10 mg/d for patients less than 10 kg. Steroids were further decreased or stopped if there was no rejection.

Prostaglandin E1 (Prostin VR; Upjohn, Kalamazoo, MI; 0.6 to 0.8 ng/kg/h) was given intravenously for at least 5 days.

Treatment of Rejection

Augmentation of the baseline immunosuppression was considered first including the addition of Azathioprine if thought to be necessary. The main indication for this was FK 506 nephrotoxicity. Depending on the severity of the rejection, a bolus of steroids or a steroid taper were also given.

OKT3 was not used in any of these cases. Graft-versus-host disease (GVHD) was diagnosed once (case 4) and treatment was unsuccessfully attempted with intravenous FK 506 and Steroids.

Prevention of Infection

All donors received polymyxin, tobramycin, and amphotericin via the nasogastric tube. The recipients received the same regimen postoperatively unless there was bacterial growth on stool cultures greater than 10^9 insensitive to these antibiotics. In these cases the appropriate antibiotics were given.

Broad-spectrum intravenous antibiotics (Ampicillin and Cefotaxime) were given to both donor and recipient, the latter for 5 days.

Nutrition

Intravenous nutrition was used liberally when enteral nutrition was not sufficient to cover the requirements of the child.

Enteral nutrition was started as soon as there was evidence of intestinal function. The solution used was full strength peptamen, (Clinitec) gradually increased in volume to cover the nutritional requirements. The volume, pH, and glucose content of the ileal output were monitored. If there was no rejection or bacterial overgrowth evident, rapid transit was treated with pharmacologic agents. If mere solidification of the stool was needed pectin was added to the peptamen.

Absorption Studies

The D-xylose absorption test was performed at least monthly. FK 506 blood levels were also used as an indicator of the absorptive ability of the intestinal graft.

RESULTS

Ten children received intestinal transplants: seven in combination with liver and three solitary. All patients who received a liver graft had advanced cholestatic disease and all had varying degrees of portal hypertension. All patients had been dependent on TPN since birth.

There were 6 female and 4 male patients. Their ages ranged between 6 months and 10 years. Intestinal failure had been caused by necrotizing enterocolitis in 3 patients, midgut volvulus in 3, and gastroschisis, intestinal atresia, microvillus inclusions disease, and intestinal pseudoobstruction (1 case of each). All had had extensive previous abdominal surgery (except patient 7) (Table 1).

Patients who underwent the combined transplant required a longer stay in the intensive care unit and developed more episodes of rejection and infections than the solitary intestinal recipients. They also required a longer time before they could be independent of intravenous feeding (Table 2).

Current immunosuppressive doses are similar in the two groups. Except for the patient in the intensive care unit (patient 10), all other patients have normal D-xylose absorption studies (Table 3).

Table 1. Clinical Characteristics and Type of Transplant

Patient No.	I	II	III	IV	V	VI	VII	VIII	IX	X
Age at TX (mo)	38	52	33	6	13	19	31	14	123	18
Primary disease	NEC	Gastroschisis	NEC	SB and colon atresia	Midgut volvulus	Midgut volvulus	Microvillous inclusions	Midgut volvulus	Intestinal pseudoobstruction	NEC
Previous surgery	SB resection, jejunostomy	SB resection	SB resection	Total enterocolectomy	SB + right colectomy, duodenostomy	SB resection	none	SB resection	Gastrectomy, colectomy	SB resection
Type of TX	LSBT	LSBT	LSBT	LSBT	LSBT	LSBT	SBT	SBT	SBT	LSBT
Date (month/year)	7/90	11/90	3/91	8/91	8/91	8/91	11/91	12/91	3/92	5/92

Abbreviations: TX, transplantation; NEC, necrotizing enterocolitis; SB, small bowel; LSBT, combined liver-intestinal transplantation; SBT, solitary small bowel transplantation.

Table 2. Postoperative Course

Patient No.	I	II	III	IV	V	VI	VII	VIII	IX	X
ICU stay (d)	4	4	3.45	23	3	130	7	5	11	Still in ICU
Hospital stay (mo)	3	3	11.5	*	6	4.3	2	2	Still in hospital	Still in ICU
Rejection (no. of episodes)	1	4	7		4	2	2	1	3	1
Infections	7	11	19		3	8	7	0	0	1
Complete enteral feeding (days posttransplant)	60	210	200		60	45	49*	14	†	

*Patient receiving a course of IV hyperalimentation supplement.
†TPN currently slowly tapered.

Two patients died, both recipients of the combined graft. Patient 3 had a complicated postoperative course, initially due to right phrenic nerve injury and paralysis of the right hemidiaphragm. Treatment required a tracheostomy and prolonged care in respiratory unit. He subsequently developed multiple episodes of rejection, treated with augmentation of the baseline immunosuppression and high-dose steroids. He later developed pleomorphic lymphoproliferative disease confirmed by allograft intestinal biopsy and died of liver failure 13 months after transplantation.

Patient 4 had IgG deficiency at the time of transplantation and was found to have *Pneumocystis carinii* pneumonitis on the second posttransplantation day. The course was further complicated by a leak from the gastro (recipient)-jejunal (donor) anastomosis. The leak was repaired and the immunosuppression reduced.

Erythema of the abdominal wall developed in the absence of further anastomotic leak. Multiple skin biopsies failed to demonstrate GVHD except on posttransplant day 21 when apoptosis was noted. Treatment was ineffective and the patient died of multiorgan failure.

Other complications included a pleomorphic lymphoma (patient 6) 9 months after transplantation and Epstein-Barr virus meningitis (patient 2) complicated by a spinal hematoma (which resulted in paraplegia) after a spinal tap.

Patient 7 developed jaundice 4 months after solitary intestinal transplantation. Cholangiography, liver, skin, rectal, and gastric biopsies have so far failed to show its cause.

All except patient 8 demonstrated a recalcitrant refusal to eat, which persisted for several months after transplantation. Patient 8 alone among the receipients was eating voraciously before transplantation.

DISCUSSION

Increasing experience with intestinal transplantation indicates that it is feasible in children, alone or in combination with the liver. It is indicated when enteral nutrition is not possible.

Adequate mapping of the pathology is important in order to ensure that the remaining viscera will perform adequately. In the present patients this was particularly true in the cases of atresia, microvillus inclusion disease, and intestinal pseudoobstruction.

To avoid the metabolic effects of the Eck fistula, a recognized complication of systemic portal drainage, hepatopetal portal venous drainage was chosen in all cases (except the native portal drainage in patient 1). Immunological advantage for this type of venous

Table 3. Current Condition

Patient No.	I	II	III	IV	V	VI	VII	VIII	IX	X
FK 506 level	1.1	0.4	Dead	Dead	1.4	0.1	2.3	0.6	1.0	Information not available
Prednisone dose (mg/d)	0	0			0	0	5	0	5	
D-xylose absorption	Normal	Normal			Normal	Normal	Normal	Normal	Normal	
FK 506 dose (mg/kg/BID)	0.1	0.1			0.3	0.1	0.6	0.12	0.2	

drainage, at least as it pertains to intestinal transplantation, has not been shown.[9-12]

The liver was replaced only when there was end-stage liver disease. It was thought that the relative simplicity and safety of solitary intestinal transplantation outweighed the potential immunologic advantage provided by contemporaneous liver transplantation. Ablation of the donor lymphatic tissue was not attempted.

It is now clear, particularly from data accumulated after intestinal transplantation, that a two-way traffic of dendritic cells and lymphocytes starts immediately after grafting.[13,14] The result is replacement of donor lymphocytes by those of the recipient and spread of donor cell colonies in the recipient's tissues.[15] The induction of this mixed chimerism is only possible under powerful immunosuppression. Manipulation of lymphocytes of either the donor or recipient could alter the balance.

The sole case of GVHD seen was probably due to inadequate immunosuppression compounded by the recipient's immune deficiency.

The results of this study imply that solitary intestinal transplantation may be equally or more efficacious than combined liver-intestinal transplantation. This experience is also supported by the results in the adult population. If confirmed it would suggest that transplantation should be performed before liver damage occurs. It is not known if and to what extent TPN-induced liver disease is reversible after successful intestinal transplantation.[3]

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