

## Isolated Small Bowel Transplantation from a Living-Related Donor at the Catholic University of Korea - A Case Report of Rejection -Free Course -

Myung Duk Lee<sup>1</sup>, Dong Goo Kim<sup>1</sup>, Sang Tae Ahn<sup>2</sup>, In Sung Moon<sup>1</sup>, Myung Gyu Choi<sup>3</sup>, Seok Gi Hong<sup>1</sup>, Sun Cheol Park<sup>1</sup>, In Sik Chung<sup>3</sup>, Jong Young Choi<sup>3</sup>, Seung Kew Yoon<sup>3</sup>, Sang Il Kim<sup>3</sup>, Jong Ho Choi<sup>4</sup>, and Eun Sun Jung<sup>5</sup>

Departments of <sup>1</sup>Surgery, <sup>2</sup>Plastic Surgery, <sup>3</sup>Internal Medicine, <sup>4</sup>Anesthesiology, and <sup>5</sup>Clinical Pathology, Organ Transplantation Center of the Catholic Medical Center, Kangnam St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Seoul, Korea.

The bowel transplantation team at the Catholic Medical Center, Korea, on April 9 2004, accomplished a case of isolated small bowel transplantation (SBT) in a 57 year-old female with short bowel syndrome. The primary surgery was a jejunocolostomy due to mesenteric vein thrombosis, while maintaining 30cm of the jejunum and colon distal to the splenic flexure. Her renal function was partially unbalanced. During more than 2 years of home TPN, the superior vena cava (VC) and subclavian veins had become occluded, but the inferior VC line remained. SBT was planned due to the repeated life-threatening infections of the last central line. One hundred and fifty centimeter of the distal ileum of the 27 year-old living-related donor, the patient's daughter, was harvested. The graft mesenteric artery and vein were anastomosed to the recipient's inferior mesenteric vessels. A proximal end-to-end jejuno-ileostomy and a distal end-to-side ileo-colostomy of the graft were made, creating a Bishop-Koop enterostomy for graft surveillance. A tube jejunostomy, via a gastrotomy, was established for early feeding and simultaneous gastric drainage. Induction with Daclizumab and immunosuppression consisted of tacrolimus and methylprednisolone, given intravenously, and then mycophenolate mofetil (MMF), enterally from day 3. The patient was discharged on day 42. A CMV infection on day 83 was successfully treated with 3 weeks of gancyclovir therapy. She has been nutritionally independent, with complete oral feeding, and free of rejection until day 170 after the transplantation.

**Key Words:** Transplantation, small intestine, living-related

Received October 6, 2004

Reprint address: requests to Dr. Myung-Duk Lee, Department of Surgery, Kangnam St. Mary's Hospital, the Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-040, Korea. Tel: 82-2-590-1345, Fax: 82-2-596-2944, E-mail: lmyungd@catholic.ac.kr

donor, short bowel syndrome

Since the early pioneering experiments conceived by Lillehei<sup>1</sup> in late 1950s, and the consecutive clinical trials, small bowel transplantation (SBT) had stayed at the experimental stage for more than two decades due to technical failures, lack of adequate immunosuppression and insufficient pathophysiology knowledge.<sup>2</sup> However, with the recent application of tacrolimus (FK-506) and accumulation of clinical experiences, SBT has evolved, over the last decade, from an experimental procedure to a precious treatment for patients with intestinal failures.

From the International Bowel Transplantation Registry,<sup>3</sup> SBT has so far been undertaken in more than 700 cases, but at less than 30 institutions and in no more than 20 countries worldwide. Recent 1 and 5 year overall patient survivals are above 60 and 45%, respectively.

We report the first experience at our institution involving an isolated SBT, from a living-related donor into an adult recipient, with short bowel syndrome due to mesenteric vein thrombosis. This is the first successful SBT reported in Korea.

### CASE REPORT

A 54 year-old female patient was referred to our institution for home TPN due to short bowel syn-

drome in October 2001. She had received a massive bowel resection due to mesenteric vein thrombosis 3 weeks prior to admission. Her remaining bowel was a 30cm section of the jejunum, which was connected, end-to-end, to the distal transverse colon (Fig. 1). The patient was managed by home TPN, via a long-term venous line (Port-a-Cath) into the superior vena cava (SVC). Recombinant human growth hormone (Eutropin inj., LG PhD, Korea), 4 IU every-other day, and 20 g oral glutamine (L-glutamine, Daesang Ltd, Korea) had been used as the treatment for a year, with remarkable nutritional adaptation. About 6-700 kcal/d of regular diet per os and 1000 kcal/d of TPN were maintained with the passing of loose stools 3-4 times.

Due to thrombotic obstruction of the SVC and subclavian veins, a new Port-a-Cath was implanted into the inferior VC on June 2003. We decided to perform a SBT, from a 27 year-old living-related donor, the patient's daughter, due to 3 repeat line infections over the previous 4 months.

**Pre-transplant preparation**

HLA typing showed an exact haplotype iden-



**Fig. 1.** Small bowel series of the recipient before transplantation. Thirty centimeter of jejunum from the Treitz-ligament (white arrow) is connected to the distal transverse colon (black arrow; jejunocolostomy site).

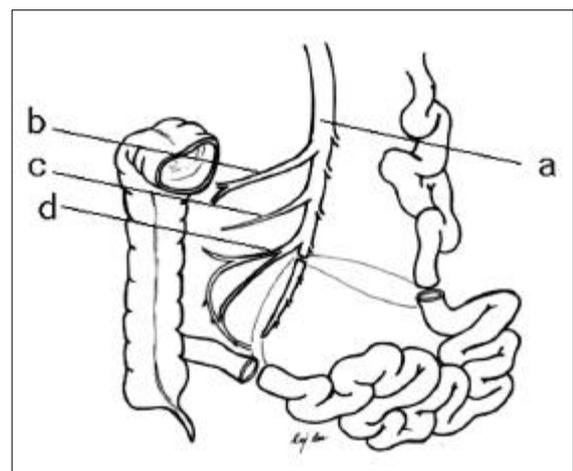
tity, as expected. Selective bowel decontamination with Ciprofloxacin (250 mg, bid. PO) and Fluconazole (50 mg, bid. PO) was administered to the donor as well as the recipient for 4 days prior to the transplantation. The immunologic studies of the CMV of the two participants were insignificant. Cow colostrum (20 g/d) and glutamine (20 g/d) given orally, and IV gancyclovir (5 mg/kg q 12 hr) were advocated from 1 week prior to surgery.

**Donor operation**

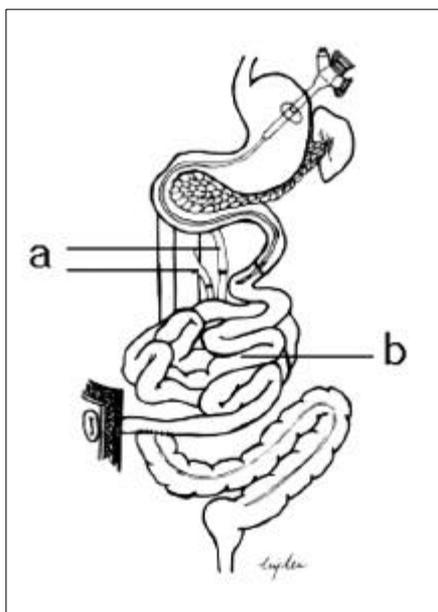
One hundred and fifty centimeter of the 5 m total small bowel was harvested. The mesenteric artery and vein of the graft were taken distal to the ileo-colic artery. Ten cm of the terminal ileum, in continuity with the ileo-cecal valve, remained for the donor, the vascularity of which was clearly secured (Fig. 2). The mesenteric cut surface was interruptly sutured for obliterating the lymphatics. Vascular perfusion, with University of Wisconsin (UW) solution (80 cmH<sub>2</sub>O by gravity), and luminal irrigation, with a UW- Ciprofloxacin mixture, through a Fr #24 catheters was performed until the out-flow was clear.

**Recipient operation**

The recipient weighed 44 kg and was 158 cm



**Fig. 2.** Donor operation. Ileocolic artery (d) and 10 cm of the terminal ileum of the donor were saved (a; superior mesenteric artery, b; mid-colic artery, c; right colic artery).



**Fig. 3.** Recipient operation. The graft mesenteric vessel anastomoses are to the inferior mesenteric vessels (a). Gastrointestinal reconstructions are also visualized (b; graft bowel).

tall. An end-to-end arterial anastomosis to the inferior mesenteric artery was performed, with 10-0 ethylon, under operative microscopy ( $\times 10$ ), with venous drainage achieved portally to the inferior mesenteric vein, end-to-end, with 7-0 prolene under loope surgery. An end-to-end proximal jejunostomy and a distal Bishop-Koop enterostomy were established, making a graft enterostomy on the right lower abdomen. A tube gastrostomy (Fr #20) for the insertion of a feeding jejunostomy tube (Fr #8) was made (Fig. 3).

### Immunosuppression

Daclizumab (interleukin-2 receptor antagonist) induction (2 mg/kg/d) was given 1 day before surgery, followed once a week for two weeks and then three times every other week after the transplantation. Prior to the operation on the day of the transplantation, the patient received an initial oral dose of tacrolimus (0.08 mg/kg BW), mycophenolate mofetil (MMF, 500 mg) and IV steroid (methylprednisolone, 400 mg). Another 400 mg of steroid was administered before reperfusion. From the time of vascular anastomosis, Alprostadil (50 mcg/d, Wel Fide Korea Co.) was

started, and continued for 10 days. Tacrolimus and steroid were given intravenously for 3 days, and then tacrolimus (0.15 mg/kg/d), MMF (500 mg/d) and steroid were taken per os.

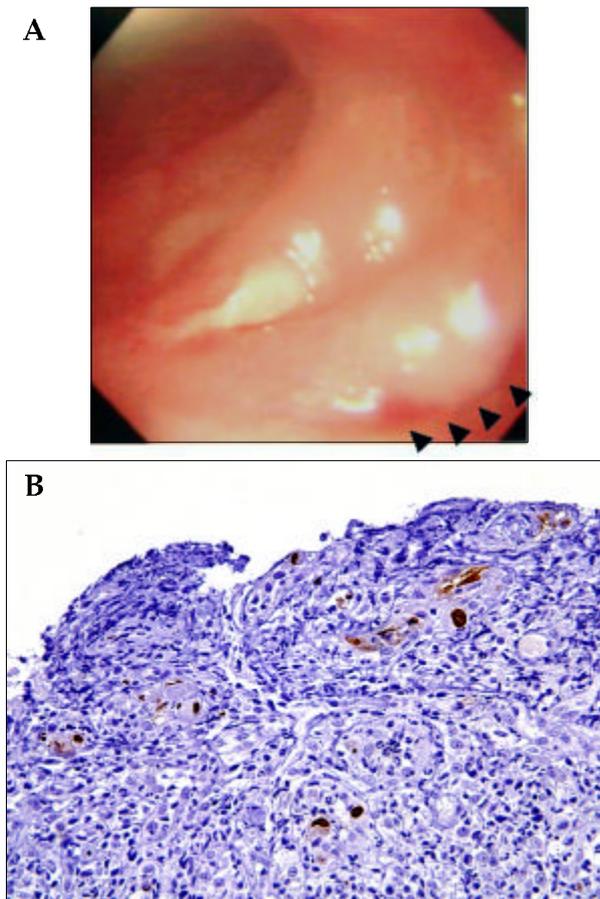
### Postoperative care

Jejunostomy feeding was started from day 5, with 25 ml/hr of 5% dextrose in water, and was increased according to the enteric condition. TPN, with Glamine (glutamine dipeptide enriched amino acids, Fresenius Kabi Korea) as an All-in-One solution (compounded in one bag with all the nutrients and IV lipid), was delivered to meet an adequate nutritional balance (1700 kcal/d). Oral supplementation of glutamine (30 g/d) and cow colostrum (20 g/d) was maintained from day 3, with Warfarin (1 mg/d, PO). Graft surveillance endoscopy was undertaken 3 times per week for the first 2 weeks, 2 times per week for the next 2 weeks, then weekly for a month, every 2 weeks for a month, and then at monthly intervals via the enterostomy, through which the stoma shape, videoscopic graft motility, villi morphology and histology were examined. Gastroscopy was applied as was required.

### Post-transplantation course

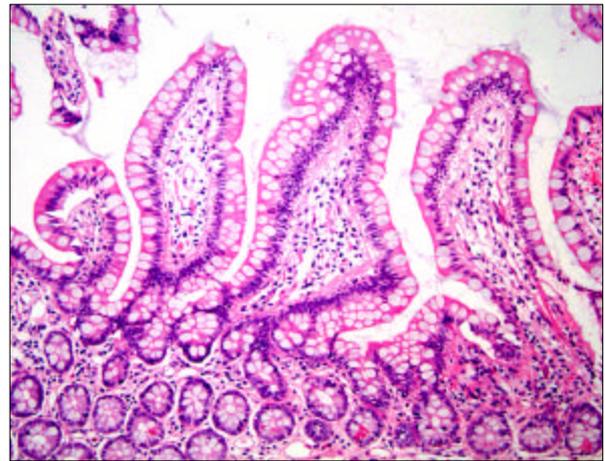
Oral feeding with low fat soft diet, enforced with MCT (10% of total diet calorie), began on postoperative day 10. The commercial polymeric diet was discontinued after the trial because of the immediate response of a high stoma output and high stool fat. Otherwise, the stoma output has remained between 500 - 800 g/d, formed in stools mixed with watery components, with or without anal passing. The gastrostomy tube, in conjunction with the jejunostomy, was removed on day 21, with sufficient oral intake. The patient was discharged 6 weeks after the transplantation, on a low fat regular diet, with intermittent IV fluid supplementation (500 - 1000 ml/d of lactated Ringer's solution and 250 ml of 20% IV lipid, 2/week), for 4 weeks.

From day 70, the MMF was ceased because of gastrointestinal discomfort, general malaise and a gastric ulcer. And the normal regular diet restored. On day 83, 3 - 5 circular ulcers on the graft around



**Fig. 4.** (A); Endoscopic finding on day 134, showing multiple circular ulcers. Arrows indicate the ileo-colostomy site. (B); Epithelial and endothelial cells having intranuclear and cytoplasmic viral inclusions, which show positive reaction for CMV antigen (Immunohistochemical staining,  $\times 400$ ).

the ileo-colostomy site were noticed (Fig. 4A), which were identified from the immunology and histology as a CMV infection (Fig. 4B). Three weeks of gancyclovir therapy was successful. On day 120, the patient complained of lower abdominal distension and heaviness due to pelvic fluid collection and chylous ascites, which were spontaneously relieved 2 weeks after returning to the low fat diet. On day 134, a catheter infection developed, so the line was removed. The patient has been nutritionally stable on a complete oral diet, and has fully recovered social and physical activities. Her present body weight is 44 kg, the same as her pre-transplant status. There were no episodes of graft rejection (Fig. 5) until day 170. Stoma closure is anticipated on day 180.



**Fig. 5.** Photomicrogram of the graft, which shows well preserved villi, without apoptosis, on day 7 (H&E,  $\times 200$ ).

The donor returned home two weeks after surgery, although suffered intermittent abdominal discomfort, followed by loose stools 3-4 times a day, until two months after the operation. Her initial 4 kg weight loss recovered after 8 weeks.

## DISCUSSION

Graft monitoring was obtained by direct visual observation of the stoma, and the amount and character of the stoma output, endoscopic morphology and motility, shape of the villi via submerged endoscopy, and the histology. About 1 m of the graft could be observed by stoma endoscopy. Video-capsule endoscopy was attempted on day 20, but failed due to the capsule captured by the foodstuff that had stagnated in the stomach. Gastroscopy showed jelly-like semi-solid contents, which were later evacuated with IV Erythromycin. Mosapride was prescribed to improve the gastric motility. The serum citrulline level showed a similar trend to the previous report by the Miami group.<sup>4</sup>

Safety of the donor and the advantages of a living-related graft in SBT have been described previously.<sup>5-7</sup> In this patient, a one-year trial of TPN taking-off procedure, with GH and glutamine,<sup>8</sup> was not completely successful; however, daily TPN doses could be reduced with dramatic improvements in anabolism and enteric absorption through the remaining short intestine. Con-

sidering the pathophysiology of short bowel syndrome, as well as the well adapted patient's own bowel, an additional length of small bowel of more than 1 m seemed to be enough to maintain her nutritional balance, even though the ileocecal valve and half of the colon were absent.

For selection of recipient vessels for reconstruction, we considered the redundancy of the vascular pedicles to be the most important for circulation safety, because of the continuous movement of the graft bowel after transplantation. Fortunately, the remaining colon showed good vascularity by clamping of the inferior mesenteric vessels, which, in this case, were utilized for graft vascular reconstruction.

The feeding of a fat-free, MCT mixed diet, supplemented by parenteral IV lipid, did not induce massive ascites in the early postoperative period. However, the restoration of a regular diet provoked chylous ascites, even 90 days after the transplantation, which is obviously later than that previously reported of Beckurts et al.<sup>7</sup> Commercially available polymers and immunonutrients can not be fitted for enteral tube feeding in SBT, due to their high fat contents, so an elemental diet is an option here. However, considering the advantages of immunonutrition, a novice immunonutrient, with low fat, is anticipated for SBT in the future. We have utilized the immunonutrition concept, with glutamine enriched TPN, enteral glutamine and cow colostrum, which contains high IgA and growth factors.<sup>9</sup> For early oral feeding, we supplied rice gruel, which contains high glutamine and slows the transit time.

With a haplotype-identical living-related donor, immunologic advantages should be expected. We recommend, as a guide, that the FK trough level between 12-17 ng/dL for 3 months, and 8-12 ng/dL for next 3 month, should be maintained,

with tapering of the steroid. Even after discontinuation of MMF, no rejection evidence at all was identified. SBT from a living-related donor, with a limited length, is effective in selected patients.

## REFERENCES

1. Lillehei RC, Good B, Miller FA. The physiological response of the small bowel of the dog to ischemia including prolonged *in vitro* preservation of the bowel with successful replacement and survival. *Ann Surg* 1959;150:543-60.
2. Kato T, Ruiz P, Thompson JF, Eskind LB, Weppler D, Khan FA, et al. Intestinal and multivisceral transplantation. *World J Surg* 2002;26:226-37.
3. Intestinal Transplant Registry (ITR). Intestinal Transplant Centers Worldwide. Retrieved on June 3, 2003, from <http://intestinaltransplant.org/>
4. Pappas PA, Tzakis AG, Gaynor JJ, Carreno MR, Ruiz P, Huijing F, et al. An analysis of the association between serum citrulline and acute rejection among 26 recipients of intestinal transplant. *Am J Transpl* 2004; 4:1124-32.
5. Benedetti E, Baum C, Cicalese L, Brown M, Raofi V, Massad M, et al. Progressive functional adaptation of segmental bowel graft from living related donor. *Transplantation* 2001;71:569-71.
6. Fujimoto Y, Uemoto S, Inomata Y, Egawa H, Fujita S, Kawanami T, et al. Small bowel transplantation using grafts from living-related donors. Two case reports. *Transpl Int* 2000;13 (Suppl 1):S179-84.
7. Beckurts KTE, Stippel D, Schleimer K, Benz C, Diens HP, Holscher AH. First case of isolated small bowel transplantation at the University of Cologne: Rejection-free course under quadruple immunosuppression and endoluminal monitoring with video-capsule. *Transpl Proc* 2004;36:340-2.
8. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. *Ann Surg* 1995;222:243-55.
9. Uruakpa FO, Ismond MAH, Akobundu ENT. Colostrum and its benefits: a review. *Nutr Res* 2002;22:755-67.