Living Related Small Bowel Transplantation

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Intestinal transplantation recently became a valid therapeutic option for patients with irreversible intestinal failure. The vast majority of the intestinal transplants have been performed using whole intestinal grafts obtained from cadaveric donors, and fewer than 10% have been performed using segmental grafts obtained from living related donors. Intestinal living donation offers several advantages, such as minimized preservation injury, eliminating waiting time, optimal donor quality and better HLA matching and possibly reduced incidence of rejection, lower immunosuppression and side effects, possibility to decontaminate the graft prior to transplantation, and possibly reduced risk of infectious complications. In the last few years, a standardized technique has been proposed for living related small bowel transplantation (LR-SBTx). Utilizing such a technique, the authors performed a series of LR-SBTx in their center and evaluated these potential advantages. In this review, the authors summarize the worldwide experience with LR-SBTx, including their own.

ABBREVIATIONS:

BT	Bacterial translocation
CMV	Cytomegalovirus
EBV	Epstein Barr virus
IF	Irreversible intestinal failure
LR-SBTx	Living related small bowel transplantatiosn
PTLD	Posttransplant lympho-proliferative disorder
SBTx	Small bowel transplantation
SBS	Short bowel syndrome
TPN	Sotal parenteral nutrition

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Background

Regardless of the etiology, irreversible intestinal failure (IF) is the condition in which absorption of fluids and nutrients from the small bowel is not adequate to sustain life. Although long-term total parenteral nutrition (TPN) is adequate to support patients with IF, it is associated with important complications such as line sepsis, venous thrombosis, and hepatic dysfunction and cirrhosis.[1] These complications are responsible for a significant mortality rate. In a recent study, patient survival on long-term TPN for nonmalignant IF has been shown to be as low as 49% at 5 years.[2] Furthermore, the quality of life of patients on TPN is suboptimal since they often do not tolerate oral diet and are limited in their activity during the infusions. Additionally, TPN is associated with high costs. In 1992 in the United States, the estimated cost per patient per year was approximately $100,000 for supplies only, not including home nursing, physician fees, laboratory costs, and expenses related to the treatment of TPN-related complications.[3]

Small bowel transplantation (SBTx) represents the physiologic alternative to TPN. Recent advances in immunosuppression, surgical technique, and postoperative management made SBTx a valid therapeutic option for patients with IF—with a 5-year intestinal graft survival up to 70%.[4]

From a report of the International Intestinal Transplant Registry, approximately 300 intestinal transplants have been performed worldwide since 1985.[5] However, the widespread application of this procedure is still limited by the relatively high rate of complications. Infections, surgical complications, acute rejection, graft versus host disease (GVHD), and posttransplant lympho-proliferative disorder (PTLD) are all observed following SBTx, with higher incidence when compared with the transplant of other organs.[6,7]

The vast majority of the intestinal transplants has been performed using whole intestinal grafts (alone or in association with liver or pancreas) obtained from cadaveric donors,[5] with or without the inclusion of the colon.[8] However, fewer than 10% have been performed using segmental grafts obtained from living related (LR) donors.

Similarly to the transplant of other organs, intestinal living donation offers several advantages, such

as reduced preservation injury, better HLA matching, and optimal donor and graft conditions. However, this procedure cannot be performed from living donors using the standardized techniques used with cadaver grafts, and a series of transplants using LR donors has not been available to unequivocally demonstrate such advantages. Moreover, LR-SBTx has not encountered initial preference among the intestinal transplant surgeons since bowel grafts are widely available from cadavers.

In the last few years, a standardized technique has been proposed for LR-SBTx.[9] Utilizing such a technique, we performed in our center a series of LR-SBTx and we evaluated these hypothetical advantages. In this review, we summarize the worldwide experience with LR-SBTx.

Worldwide Experience with LR-SBTx

The reported data on worldwide experience with LR-SBTx are summarized in Table 1. Initial attempts were reported in the 1960s and 1970s from Boston, Mississippi, and New York.[10,11] In Boston, a pediatric recipient was transplanted using a segment of ileum donated from the mother and died 12 h after the procedure. From the same group, a second attempt was mentioned during the discussion of a scientific meeting, but neither of these cases was ever published.

In Mississippi, 100 cm of distal ileum was transplanted in a pediatric recipient. The graft was removed 9 days later for extensive necrosis, and the patient died shortly thereafter.

The group in New York transplanted 170 cm of jejunum and ileum between HLA identical sisters. The recipient survived 79 days, and she was able to tolerate oral diet for approximately 6 weeks.[12] The immunosuppression used has not been reported by all these centers with the exception of New York and Mississippi where azathioprine, prednisone, and ALG were used. Although technically feasible and promising, this procedure remained a unique challenge mostly because the immunosuppression available at the time was inappropriate. The introduction of TPN in 1968 further reduced the interest in clinical SBTx.[13] The intestine was considered the "untouchable" organ for transplant surgeons for approximately 20 years, while other solid organs were transplanted worldwide with enormous interest and impressive results in terms of graft and patient survival.

The introduction of cyclosporine elicited a new burst of interest for this procedure in the 1980s. A German group led by Deltz was the first to report a successful clinical LR-SBTx in 1988. They used a 60-cm segment of distal jejunum and proximal ileum donated by the half sister of the recipient who survived 4 years on oral diet.[14] A previous unsuccessful attempt was performed 10 months earlier by the same group in a pediatric recipient. The 60-70 cm jejunum/ileum graft, obtained from the mother, was unfortunately rejected 12 days after the procedure.[15] The immunosuppressive regimens used in these cases were based on cyclosporine, steroids, and ATG.

In the 1990s, a new impulse for SBTx was given by the introduction of FK-506, and LR-SBTxs were performed in 5 centers.[16] Pollard in the United Kingdom successfully transplanted a segment of 180 cm of ileum from the mother to the daughter. This patient had several episodes of rejection and died 18 months later from pneumonia.[17] Morris, in California, reported the transplant of a segment of 110 cm of distal ileum, ileocecal valve, and cecum between twin brothers. Survival has been reported up to 1 year.[18] The group in New Orleans, lead by Jaffe, performed 2 transplants between mother and offspring using 200 cm of jejunum. These patients had rejection and infectious complications. Survival up to 1 year has been reported.[19] In Minneapolis, Gruessner performed 2 successful LR-SBTx from parent to offspring using approximately 200 cm of distal ileum. The author was the first to describe in detail the donor work-up and the surgical technique used to establish a standardized approach for LR-SBTx.[9] The Japanese group of Fujimoto and Tanaka performed 2 pediatric transplants between mother and offspring using 100 to 120 cm of terminal ileum. Both patients had several episodes of rejection. One of them died 16 months after the transplant owing to *Pneumocystis carinii* pneumonia, whereas the other was reported alive at a 14-month follow-up.[20]

In 1998, the first successful transplant was performed in our institution. In the following years, we performed a total of 4 adult LR-SBTx (Table 2).[21] In our experience, the graft used was always 180 to

Table 1 | **Living Related Small Bowel Transplantation—Worldwide Experience**

Year/Place/Author/Ref.	Recipient Age (yrs.)/Sex Cause of IF	Donor HLA Match	Utilized Graft (Cold Ischemia Time)	Immunosuppression	Outcome
1964 Boston (USA)[10]	• ? • Child	• Mother • ?	Ileum	• ?	• Death 12 h after Tx
1964 Boston (USA)[10]	• ? • ?	• ? • ?	?	?	• Death
1969 Jackson at Mississippi (USA)[11]	• 8/male • Illeal strangulation	• Mother • Class B (Terasaki Scale)	100 cm distal ileum (75 min)	• AZA • Antilymphocyte globulin • Prednisone	• Graft removed at POD 9 for extensive ischemic necrosis • Sepsis and death on POD 30
1972 New York (USA)[12]	• 37/female • Gardner's syndrome	• Sister • Identical	170 cm lower jejunum and upper ileum (110 min)	• AZA • Antilymphcyte globulin • Prednisone	• 1 severe acute rejection • Eating for 6 weeks • Death 76 days after Tx with *E. coli* sepsis
1987 Kiel (Germany)[15]	• 4/male • Volvulus	• Mother	60 cm from the medium jejunum (80 min)	• ATG • CsA • Steroids	• Acute rejection after graft loss 12 days after Tx
1988 Kiel (Germany)[14]	• 42/female • SMV and IMV thrombosis	• Half sister • Haploidentical	60 cm lower part jejunum and upper ileum (75 min)	• ATG • CsA • Steroids	• 4 acute rejection episodes • TPN free for 4 years when graft loss due to acute and chronic rejection • Died 5 yrs after Tx
1995 Leeds (UK)[39]	• 28/female • Gardner's syndrome and desmoid tumor	• Mother • Haploidentical	180 cm distal ileum (less than 30 min)	• FK506 • Steroids • AZA	• 3 episodes of acute rejection at 1, 3, and 10 weeks after Tx • 1 episode of acute rejection was associated to candida infection • Death at 18 months from severe pneumonia
1995 Stanford California (USA)[18]	• 34/male • Desmoid tumor	• Twin brother • Identical	Distal ileum, ileocecal valve and portion of the caecum (110 min)	• None	• Sepsis-like syndrome on POD 4 • Alive and TPN free at 1-year follow-up
1995 New Orleans Louisiana (USA)[19]	• 26/female • Gardner's syndrome	• Mother • Haploidentical	200 cm proximal jejunum	• OKT3 • FK506 • MMF • Prednisone	• Loss of 20 cm of graft on POD 7 (ischemic necrosis) • Severe acute rejection 7 months after Tx • Need of night TPN after 6 months
1996 New Orleans Louisiana (USA)[19]	• 29/male • Ganglioneuropathy	• Mother • Haploidentical	180 cm jejunum	• OKT3 • FK506 • MMF • Prednisone	• Jejunocolostomy leakage on POD 18 • 2 episodes of rejection 3 months after Tx • 4 episodes of bacterial overgrowth • 2 episodes of CMV infection • 1 candida sepsis from invasive fungal duodentitis • Need of TPN 7 months after Tx

1996 Kyoto (Japan)[20]	• 2.5/male • Volvulus	• Mother • Haploidentical	100 cm distal ileum	• FK506 • Steroids • AZA	• 4 episodes of acute rejection followed by line infection, EB, CMV • Patient had been on TPN for almost his entire post-Tx course • Death after 16 months due to Pneumocyst carinii infection
1997 Minneapolis Minnesota (USA)[9]	• 17/male • SMA injury	• Father • 4	200 cm distal ileum	• OKT3 • FK506 • MMF • Prednisone	• Alive and TPN free at 18-month follow-up
1997 Minneapolis Minnesota (USA)[9]	• ? • Chron	• Mother	200 cm distal ileum	• OKT3 • FK506 • MMF • Prednisone	• Alive and TPN free at 1-month follow-up
1997 Cambridge (UK)[22]	• 40/male • SMV thrombosis	• Twin brother • Identical	150 cm distal ileum	• None	• Alive and TPN free in 1997
1999 Kyoto (Japan)[20]	• 4.5/female • Midgut volvulus	• Mother • Haploidentical	120 cm distal ileum	• OKT3 • FK506 • Steroids • Cyclophosphamide	• 4 episodes of acute rejection • Line infection during acute rejection • EBV and CMV enteritis • Alive and TPN free at 14-month follow-up
1999 Geneva (Switzerland)[23]	• 13/male • Midgut volvulus	• Twin brother • Identical	160 cm midileum	• None	• Line infection sustained by Staphylococcus aureus • Alive and TPN free at 14-month follow-up
1999 Xi'an[24]	• 18/male	• Father	150 cm distal ileum	• PK506 • MMF • Prednisone	• HSV infection, intestinal hemorrhage and line sepsis after 1 month • 1 episode of acute rejection • Alive and TPN free at 4-month follow-up

Table 2 | **Our Experience at the University of Illinois at Chicago**

Year	Recipient Age (years/sex)	Cause of IF	Donor/ HLA Matching	Graft	Immunosuppression	Outcome
1998	27/male	Trauma	Twin sister 6 antigens	200 cm distal ileum	FK506, ATG, Steroids	• 1 CMV gastritis episode • Alive and TPN free at 36 months
1999	29/male	Trauma	Father 3 antigens	200 cm distal ileum	FK506, ATG, Steroids	• 1 CMV enteritis episode • Alive and TPN free at 24 months
1999	46/male	SMA	Son 5 antigens	200 cm distal ileum	FK506, ATG, Steroids	• Acute pancreatitis, graft removed 6 weeks after Tx • Death after 12 months for TPN induced liver failure
2000	30/male	Trauma	Brother	200 cm distal ileum	FK506, ATG, Steroids	• Alive and TPN free at 6 months

200 cm of distal ileum, donated by a family member (brother, sister, father, and mother) with excellent HLA matching (3 to 6 antigens). Three of these patients are currently alive, TPN free, and back on regular daily activities with a follow-up of 6, 21, and 36 months. No episodes of rejection or severe infectious complications have been observed. Only 1 patient developed CMV enteritis and was treated with IV ganciclovir. In the 4th patient, we had to remove the graft 6 weeks after the transplant following ischemia, probably due to octreotide treatment for severe pancreatitis. The graft had patent blood vessels and did not present immunologic or infectious complications. The patient returned to TPN and died 1 year later for TPN-induced liver failure.

Three additional successful cases have been reported worldwide in the last few years. The Cambridge group performed 1 transplant between 2 identical triplets, using a segment of 150 cm of distal ileum and no immunosuppression.[22] Morel's Swiss group performed a transplant between monozygotic twins using 160 cm of mid ileum.[23] Also, a Chinese group, headed by Wang, performed an LR-SBTx between father and son using a segment of distal ileum.[24]

Surgical Technique and Considerations

As mentioned above, cadaveric intestinal transplantation is performed using the whole intestine, whereas the LR intestinal transplant implies the use of a portion of the small bowel. It is possible to utilize segmental jejunal or ileal grafts, and both techniques have been used. However, the vascular supply of the terminal ileum offers a convenient pedicle for the graft, and this technique has been standardized. In addition, the distal ileum allows the absorption of vitamin B12, bile salts, and unlike the jejunum, a better absorption of water and solutes and is known to ensure adequate morphologic adaptation.[25]

The approach used in our experience for LR-SBTx implies a careful donor selection. These should be young, healthy individuals for whom preoperative angiogram of the superior mesenteric artery excludes abnormalities of the vascular supply to the cecum, ileocecal valve, and terminal ileum. Furthermore, an optimal HLA matching between donor and recipient is recommended and donors should be selected, if possible, among multiple candidates accordingly. The preoperative graft decontamination is obtained with standard mechanical bowel preparation and antibiotics. A segment of 180 to 200 cm of ileum is resected 15 cm from the ileocecal valve that is spared in the donor to reduce the risk of diarrhea and liposoluble vitamin absorption impairment. In our experience, the length of the graft obtained is decided in relationship to the total length of the donor small bowel. The vascular pedicle of the graft is obtained dissecting the ileocolic vessels immediately distal to the origin of the right colic artery that is carefully preserved to maintain vascular flow to the right colon. The mesenteric peritoneum is scored, and the vessels are identified and dissected up to the origin of the ileocolic vessels. Once the segment of ileum is removed, the

remaining intestinal segments are primarily reanastomosed in end-to-end fashion using 4-0 polyglyconate for the mucosal layer and 4-0 polypropylene for the seromuscular layer. Following vascular flush with chilled University of Wisconsin solution, the segmental graft is transplanted suturing the ileocolic vessels in an end-to-side fashion to the infrarenal aorta and inferior vena cava of the recipient using 6-0 polypropylene. Using this technique, the cold ischemia time is approximately less than 10 min and the warm ischemia time is 30-40 min. The intestinal continuity is immediately reestablished anastomosing the graft to the recipients' intestinal stumps using 4-0 polyglyconate for the mucosal layer and 4-0 polypropylene for the seromuscular layer. A temporary distal loop ileostomy is performed to monitor graft output and to perform endoscopic biopsies to evaluate rejection or viral infections. Perioperative recipient prophylaxis for infectious complications is accomplished with vancomycin (1 g IV at induction of anesthesia), piperacillin (3 g IV 6-8 times a day, adjusted for renal function, for 3 days), and ganciclovir (5 mg/kg IV every 12 h for 14 days) followed by acyclovir (800 mg PO 4 times a day for 3 months).

Our immunosuppressive protocol consists of oral tacrolimus and prednisone. Intravenous induction with atgam is used until therapeutic blood levels of tacrolimus are achieved.

Discussion

LR-SBTx offers several advantages compared with cadaveric SBTx. This is an elective procedure and can be performed when the donor and recipient conditions are optimal and donor bowel decontamination can be easily performed. This should result in a decreased risk of early infectious complications. In a previous study on recipients of cadaveric grafts, we showed that the length of preservation was a significant factor in inducing perioperative bacterial translocation (BT).[26] With cadaveric intestinal transplant, such risk cannot be avoided since hemodynamic instability of the donor and subsequent splancnic hypoperfusion can trigger ischemic damage even before the intestine is procured.[27] Furthermore, bowel decontamination in the donor is not feasible and these grafts are often subject to prolonged cold preservation while specific preservation solutions designed for intestinal grafts are not yet available. In a recent study, we also showed that ischemic injury induces chronic morphologic alterations of the intestinal mucosa.[28] An additional advantage of LR-SBTx is that the availability of a living related donor allows minimization of transplant waiting time, thus reducing the evolution of TPN-related complications, such as liver damage.

An immunologic advantage is also obtained with LR-SBTx, since optimal HLA tissue matching can be obtained between donor and recipient that are related. It is a common belief that HLA matching is not important in SBTx, and this is possibly consequent to the frequent association of bowel-liver transplantation. However, no data are available from cadaveric SBTx to confirm such a belief—and a high rate of rejection, approximately 90%, have been reported in these patients.[29-31] In our opinion, liver and intestinal grafts behave differently from an immunologic standpoint. In our experience with well-matched donor-recipient combinations, we have not seen rejection using an immunosuppressive regimen based on tacrolimus and prednisone. Furthermore, other groups reported LR-SBTx successfully performed between twins with low or no immunosuppression. This seems to confirm the importance of tissue matching in intestinal transplantation and, thus, should also be obtained in cadaveric SBTx since intestinal graft donors are widely available. From this experience, we adopted the strategy in our cadaveric intestinal transplant program to minimize the preservation time and to use well-matched, hemodynamically stable donors.

This strategy allows a reduction of the immunosuppression, with the consequent benefit of fewer related complications. This is of particular importance since cadaveric SBTx is reportedly burdened by a high rate of PTLD up to 20%, which is higher than observed in any other organ transplant.[32] Although unlikely in cadaveric SBTx, no cases of PTLD have been reported in LR-SBTx recipients.

An additional advantage of segmental grafts is that their smaller size allows them to be transplanted in patients with a retracted abdominal cavity. This can be due to multiple laparotomies, loss of abdominal wall, or severe intra-abdominal adhesions.

A potential disadvantage of LR-SBTx is the surgical risk for the donor. However, this is low if associated

with elective small bowel resection and primary anastomoses in otherwise healthy individuals, especially when the procedure is performed by experienced surgeons. To date, no surgical complications or deaths have been reported for LR intestinal donors. Furthermore, according to the available literature, it does not appear that the donor will suffer long-term absorption problems with ileal resection limited to approximately 200 cm.[9,14,17,19-21] Mild occasional diarrhea can be observed only in the early postoperative time and is well controlled with medical therapy, with no evidence of vitamin B_{12} absorption deficit or weight loss, in our experience. Additionally, to our knowledge, no long-term impairment of intestinal absorption in bowel donors has ever been reported.

An additional disadvantage of using intestinal grafts obtained from living donors rather than cadavers is the technical difficulty in using smaller diameter vessels for the vascular anastomoses. This is particularly true if the segment used is jejunum. As reported in the literature, the use of jejunum often requires multiple vessels as vascular pedicle, making the operation more challenging and increasing the risk of thrombosis or chronic hypoperfusion of the graft.[19] In our experience, we utilized a single ileocolic artery and vein, performing the arterial anastomosis with interrupted technique to minimize such risks and did not witness any of these complications.

It can be argued that the use of a shorter segment of bowel in LR-SBTx may not be sufficient to provide an adequate absorption of nutrients. From the literature, most of the surgeons performing LR-SBTx have used segmental grafts of 160 to 200 cm. The decision on how to select an optimal length of bowel is purely empiric. However, it is based on the knowledge that a segment of 50 cm of small intestine will not allow sustaining of life with enteral alimentation.[33-35] Considering that the graft can undergo injury for manipulation, preservation, and rejection, we believe that it is safe to use a segment of 180 to 200 cm of ileum. The choice of this length also ensures that the donor is left with a segment of at least 300 cm of native small bowel and terminal ileum that are not subject to similar damages. Furthermore, the preservation of the ileocecal valve in the donor contributes to reducing postresection dehydration. In our experience, the segmental grafts underwent complete functional adaptation within 6 months. These patients were TPN free immediately after the transplant and able to regain—and maintain—preintestinal failure body weight and serum albumin levels with oral diet.[36]

After cadaveric SBTx, bacterial, fungal, and viral infections are quite common. The incidence of such complications is higher than any other organ transplant, probably due to the need for more vigorous immunosuppression. Infectious complications are the most common cause of death and graft loss, accounting for up to 69% of patient loss after cadaveric SBTx.[37] Line infections, sepsis, abdominal fungal infections, and viral infection or reinfections (EBV and CMV) are also reported after LR intestinal transplantation. Although less frequent than cadaveric SBTx, severe infections leading to recipient death have been reported.[19,20] Several authors speculate that some of these infectious complications originate from bacterial translocation of enteric flora during rejection episodes.[17] Recently, we analyzed the number of bacterial translocation episodes (evaluated by the simultaneous presence of a specific microorganism in the stool and other sites) in 50 pediatric SBTx recipients.[26] This analysis showed that 44% of patients had at least one episode of BT associated with rejection and cold preservation. In a recent analysis of our LR-SBTx experience, we observed a very low rate of infections and no episodes of BT.[38] It is difficult to extrapolate any conclusion since our experience is limited, but the absence of bacterial infections and the low rate of viral complications observed suggest an advantage to this approach. Several factors might have contributed in this regard, such as hemodynamic stability of donors and recipients, optimal graft decontamination, minimization of preservation injury, and reduced immunosuppression. However, it is impossible to identify which of these factors plays a dominant role and probably they all contribute in part to reducing BT and infectious complications in LR-SBTx.

Despite all these considerations, several attempts performed worldwide with LR-SBTx have been unsuccessful. However, long-term patient and graft survival were achieved with LR-SBTx, even in the pre-tacrolimus era in some patients, probably due to some degree of immunologic advantage obtained

with the tissue matching. Another limitation of the reported experience with LR-SBTx is the dishomogeneity of the cases. Often, these were performed as isolated attempts by each group, making it impossible for the surgeon to overcome an unavoidable learning curve. Furthermore, different surgical techniques were often used as well as different immunosuppressive regimens (Table 1). In our experience, we used a standardized approach to evaluate the potential advantages of LR compared with cadaveric SBTx.

In conclusion, intestinal living donation offers several advantages, such as minimized preservation injury, eliminating waiting time, optimal donor quality, and better HLA matching and reduced incidence of rejection, lower immunosuppression and reduced associated side effects, possibility to decontaminate the graft prior to transplantation, and reduced risk of infectious complications. From the reported cumulative experience, LR-SBTx reached a 1-year survival rate of approximately 50%. Evaluating the reported cases in the tacrolimus era, the survival rate at 1 year goes up to approximately 70%. In our opinion, these rates are not reflecting the real potential of the procedure. As we already discussed, different groups utilized many different approaches, creating confusion without gaining extensive experience. We suggest that a standardized approach should be used for LR-SBTx. In our limited but significant experience with this procedure, we are confident that LR-SBTx is a valid alternative to cadaveric SBTx.

Significant advantages offered by this approach such as short ischemia time, HLA match, and selection of hemodynamically stable donors should be, in our opinion, adopted for cadaveric intestinal transplantation as well.

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