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The Role of Intestinal Transplantation in the Management of Babies With Extensive Gut Resections

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Background/Purpose: Modern neonatal care, surgical treatment, and total parenteral nutrition (TPN) have improved survival rate for babies with extensive gut resections. The authors examined the role of intestinal transplantation in the treatment of these patients.

Methods: The authors reviewed all pediatric intestinal transplants performed for short bowel syndrome at our center (70 transplants performed between Aug 1994 and Feb 2002). Factors affecting patient survival were analyzed.

Results: Older patient age at the time of transplant was a significant factor favorably affecting patient survival (P = .031). Trends toward better survival rates were observed in those transplants performed more recently (P = .063), in those patients with greater body weight (P = .084), in those not hospitalized at the time of transplant (P = .14), and in those without concomitant liver failure (P = .12). Three-year survival rate for patients greater than age 2 years and without liver failure was 90%. However, 32% of our recipients underwent transplant at age less than one year, and most in this group (75%) had concomitant liver failure.

Conclusions: For babies with irreversible intestinal failure, intestinal transplantation is a life-saving option. Results, which have recently improved, are best when transplantation compliments more conservative surgical treatments and TPN. However, there is a subset of patients who have liver disease early requiring urgent transplant.

INDEX WORDS: Intestinal transplantation, short bowel syndrome.

ADVANCES in neonatal care, early surgical intervention, and total parental nutrition (TPN) have improved dramatically the outcome for infants with extensive bowel resection.[1-11] Most of these infants can experience bowel adaptation during the first few years of their lives.[12-14] However, there is a group of patients who become chronically TPN dependent. Some eventually have serious complications from TPN such as progressive cholestatic liver disease, loss of venous access, or repeated episodes of central line related sepsis. In addition, there is a subset of infants who do not tolerate TPN and have life-threatening complications at an accelerated rate. These patients typically present with liver failure within the first year. Intestinal transplantation has been performed in these children as a life-saving option.[15,16,20-23] As results for intestinal transplant continue to improve, it has been adopted as one of the options in the management of infantile short bowel syndrome. We herein describe our center's experience with 70 cases of pediatric intestinal transplants in babies with extensive bowel resections to clarify the role of transplantation in the management of intestinal failure.

MATERIALS AND METHODS

We performed a retrospective review of the medical records of all children who underwent intestinal transplantation at the University of Miami/Jackson Medical Center, Miami, Florida since 1994. Of 86 transplants performed, 70 cases were performed in children who had a

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history of extensive bowel resection. These cases were analyzed. Intestinal transplants performed for children with functional abnormalities of the intestine such as microvillus inclusion disease, megacystis microcolon syndrome, and chronic pseudoobstruction syndrome were not included in the analysis. Data collected included reason for extensive bowel resection, age and body weight at the time of transplant, hospital bound or home immediately before the transplant, presence of concomitant liver failure, types of graft received, year transplanted, length of follow-up, and patient and graft survival. We also identified 19 patients who died before transplant (8 died after being placed on the waiting list, 11 died before the listing) during the same period. The causes of death in the 8 patients who were on our waiting list were reviewed.

Transplant procedures were performed as previously described.[15] Several modifications of our postoperative protocols were made in the beginning of 1998. Before 1998, postoperative surveillance endoscopy and biopsy to detect rejection were performed only when rejection was suspected. Also, Cytomegalovirus (CMV) seropositive donors were used only in emergency cases based on the observations of another investigator that their use was associated with higher mortality rate.[16] After 1998, protocol surveillance with zoom endoscopy and biopsy was started, and CMV-positive donors were used routinely with an improved antiviral regimen.[17,18] Baseline immunosuppression included tacrolimus and corticosteroids in all cases. Additional agents were used for induction: OKT3, 1994; cyclophosphamide, 1995, mycofenolate mofetil 1996 through 1997; daclizumab, 1998 to present, Campath 1H 2001 to present. Patients with Campath 1H did not receive maintenance corticosteroids except for the treatment of rejection.

Factors affecting patient survival rate were analyzed by the Cox proportional hazard regression model. A P value of less than .05 was deemed statistically significant. Log-rank test was used to compare survival curves. The analyses were performed with a computer software (Statistical Package for Social Science, SPSS Inc, Chicago, IL).

RESULTS

Seventy intestinal transplants were performed in 63 children during the study period. Six patients received retransplants; one of them received 2 retransplants. There were 36 boys and 27 girls. Median age at transplant was 1.6 years (range, 7 months to 13 years). Twenty patients (32%) were less than one year old at the time of transplant. Median body weight at the time of transplant was 9.5 kg (range, 4.5 kg to 38 kg). The causes for short bowel syndrome included necrotizing enterocolitis (n = 16), gastroschisis (n = 20), intestinal atresia (n = 9), volvulus (n = 9), Hirschsprung's disease (n = 6), and others (n = 3). All patients were chronically dependent on TPN. Indications for transplant were liver failure in 43 patients (68%), development of cholestatic liver disease in 2 (4%), loss of venous access in 8 (12%), and recurrent central line–related sepsis in 10 patients (16%). The liver was included in the graft only for patients with liver failure. Liver failure was the indication for transplant in 15 of 20 children less than one year of age (75%). Thirty four patients were at home when a donor became available, 18 were in the regular hospital ward, and 11 were in the intensive care unit. Patients' characteristics are summarized in Table 1.

Table 1. Baseline Characteristics of 63 Patients

Factor	Ratio	Percent	Median	Mean ± SD
Age			1.6	3.12 ± 3.3
Age>2yr/≤2yr	26/37	41/59		
Age>3yr/≤3yr	19/44	30/70		
Sex (M/F)	36/27	57/43		
Weight (kg)			9.5	12.8 ± 1.1
Weight >10 kg/≤10kg	35/28	55/45		
Weight >8 kg/≤8kg	42/21	66/34		
Weight >7 kg/≤7kg	49/14	77/23		
Weight >6 kg/≤6kg	55/8	87/13		
Weight >5 kg/≤5kg	59/4	94/6		
Etiology of resection				
NEC	16			
Gastroschisis	20			
Volvulus	9			
Intestinal atresia	9			
Hirschsprung disease	6			
Others	2			
PreTx status				
Home/Hosp/ICU	34/18/11	54/28/18		
Home/hospital	34/29	54/46		
Era				
94-97/98-00/01-	19/28/23	27/40/33		
Concomitant liver failure				
Yes/No	44/26	63/37		

NOTE. Total of 63 patients, 70 cases (7 retransplants).
Abbreviations: NEC, necrotizing enterocolitis; Tx, transplant.

Nineteen cases were done during the period between 1994 and 1997, 28 were done between 1998 and 2000, and 23 after January of 2001. Transplant types included isolated intestine (n = 21), liver and intestine (n = 25), and multivisceral transplant (en bloc transplant of stomach, pancreas, liver and intestine n = 23). In 16 cases of liver and intestine transplants, donor pancreas and duodenum were included in graft as described previously.[19] Baseline immunosuppression was tacrolimus and corticosteroids in all cases except for patients who received Campath 1H induction. Adjuvant agents for induction immunosuppression included OKT 3 (n = 3), cyclophosphamide (n = 3), mycophenolate mofetil (n = 13), daclizumab (n = 45), and Campath 1H (n = 6).

Thirty-three patients (52%) currently are alive at a median follow-up of 327 days (range, 47 to 2,527 days). Short-term survival rate has improved in recent years (Fig 1). Patient survival at 6 months, one year, and 2 years was: 55%, 50%, and 38% in the period between 1994 and 1997; 58%, 50%, 46% in 1997 through 2000; 86%, 86%, and NA in 2001 to present. Five isolated intestine recipients underwent graft enterectomy, 4 because of severe rejection and one because of chronic rejection. Three of them have undergone retransplant, 2 currently are alive, and the other died after retransplant. One patient currently is waiting for retransplant. The remaining 2 patients died without retransplant. These 2 deaths are included as patient deaths in this study. Of the patients who underwent retransplant after receiving

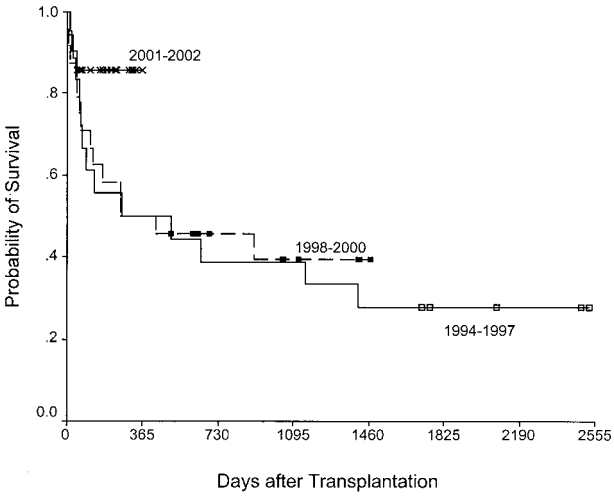

Fig 1. Patient survival rate in 3 different eras. Comparison among 3 different periods (1994 through 1997, 1998 through 2000, and 2001 to present)

grafts including the liver, all retransplants were done at the time of graft removal. All but one of these recipients died after retransplant. One survived after 2 retransplants with multivisceral grafts. All survivors in our series, except for one who is waiting for retransplant, have been weaned off TPN and receive all their nutritional requirements via the intestinal graft.

The causes of death were rejection (n = 6), sepsis/MSOF (n = 7), viral pneumonia (n = 4), necrotizing fasciitis (n = 2), posttransplant lymphoproliferative disease (PTLD; n = 2) and graft-versus-host diseases (GVHD; n = 1). PTLD was observed in 5 cases. Three patients were treated successfully by reduced or discontinuation of immunosuppression and prolonged use of monoclonal antiCD 20 antibody, rituximab (Rituxan, Genentech, San Francisco, CA). GVHD was observed in 5 cases. All but one patient responded to steroid therapy. One patient died of chronic lung disease caused by GVHD.

Factors affecting patient survival were determined by univariate analysis. Variables analyzed included age at the time of transplant (as a continuous parameter, ≤ 2 *v* >2, ≤ 3 *v* greater than 3), body weight at the time of transplant (as a continuous parameter, ≤ 10 kg *v* >10 kg), pretransplant status (hospitalized immediately before transplant *v* at home), and presence of concomitant liver failure (Table 2, Fig 2). The significant factors adversely affecting survival were younger age (as continuous variable) at the time of transplant ($P = .031$), age less than or equal to 3 years ($P = .035$), and hopitalized in regular ward immediately before transplant ($P = .011$). There were trends toward worse survival rate in cases of body weight ≤ 10 kg ($P = .084$), concomitant liver failure ($P = .12$), hospitalized (regular ward or ICU; $P = .14$). Location in the ICU pretransplant did not affect survival if transplanted. When age and the presence of liver failure are combined, survival rate is significantly better in patients older than age 2 without liver failure compared with patients younger than age 2 with liver failure (Fig 2C; $P = .016$).

All 19 patients who died before transplant had concomitant liver failure at the time of referral. Six of 8 patients who died on the waiting list died of multisystem organ failure and gastrointestinal bleeding.

DISCUSSION

Intestinal transplantation can be a life-saving option for patients with short bowel syndrome and serious complications of TPN.[15,16,20-23] Complications from TPN that could be life threatening are liver failure, loss of venous access, and central line–related sepsis. Although intestinal transplantation has been more recognized as a viable option in the management of intestinal failure in infants and children, the best time to consider a transplant has not been established.

Extensive bowel resection or congenital malformation of the small bowel are the causes of short bowel syndrome in infancy and childhood. Common etiologies include necrotizing enterocolitis (NEC), gastroschisis, intestinal atresia, volvulus, and extensive Hirschsprung's disease.[4-11] With recent advances in TPN and the management of central venous catheters, these patients can be stabilized with TPN while waiting for intestinal adaptation.[1-3] By age 3, many children can be weaned off TPN because of the adaptive capabilities of the gut.[12-14]

Table 2. Relative Risks for Postoperative Mortality in 63 Intestinal Transplant Recipients

Factor	Odds Ratio	95% CI Lower	95% CI Upper	*P* Value
Age				
continuous	**0.845**	**0.725**	**0.985**	**0.031**
>2 years	0.505	0.235	1.084	0.080
>3 years	**0.380**	**0.154**	**0.936**	**0.035**
Weight				
continuous	0.949	0.895	1.007	0.084
>10kg	0.612	0.285	1.312	0.207
Concomitant liver failure	2.029	0.825	4.989	0.123
Era (Era 1, 94-97; Era 2, 98-00; Era 3, 01-02)				
Era 3 (compare with era 1+2)	0.316	0.094	1.061	0.062
Era 3 (compare with era 1)	0.296	0.082	1.006	0.063
Era2 (compare with era 1)	0.891	0.416	1.91	0.767
Preoperative status				
Home (compare with other)	0.577	0.276	1.206	0.144
Hospital (compared with home)	**2.725**	**1.255**	**5.919**	**0.011**
ICU (compared with home)	0.685	0.195	2.405	0.555

NOTE. Proportional hazard (cox) regression. Total 63 cases, censored 33 cases. Factors with $p < .05$ are highlighted.

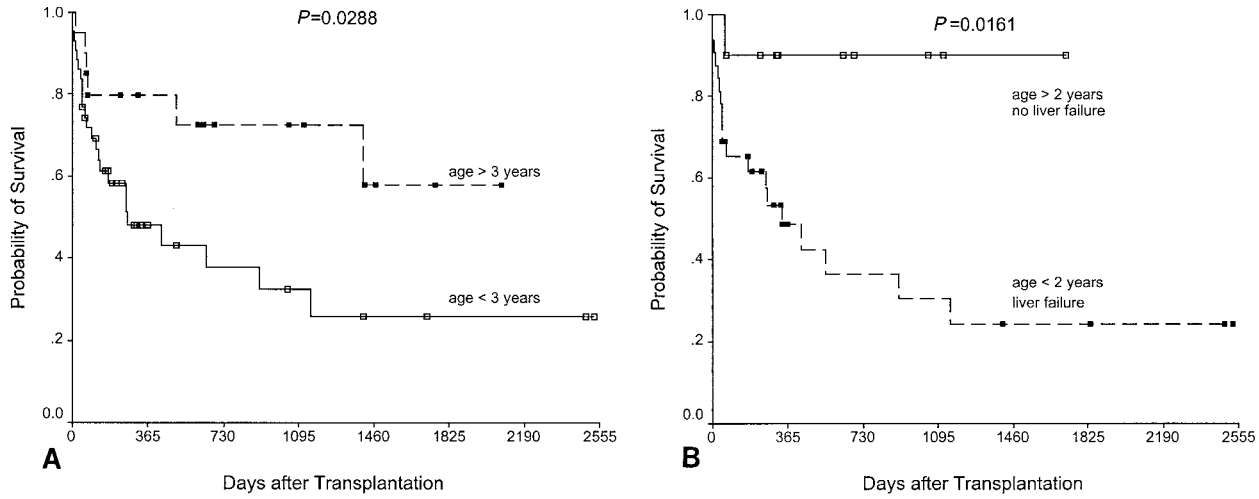

Fig 2. Factors affecting survival. (A) Comparison of survival probability of patients between age group. (B) Combined age and concomitant liver failure.

The predictors of permanent TPN dependency suggested by other investigators are short length of residual bowel, absence of the ileocecal valve, and inability to tolerate enteral caloric intake.[12-14] When patients do not adapt adequately, long-term use of TPN may cause serious side effects.

In this study, we attempted to delineate the role of intestinal transplant in the management of short bowel syndrome in infants and children. Recipient age at the time of transplant is a significant factor affecting survival ($P = .032$). Transplantation should be delayed, if possible, until the child is older and has grown. However, waiting may increase the risk of catheter-related complications and TPN-induced liver dysfunction. To our surprise, being located in ICU pretransplant did not affect survival rate, but being in a regular hospital ward did. It may be explained that the patients who require chronic regular ward hospitalization are more prone to hospital-acquired infections. The reason being located in ICU did not affect survival is unclear, but it may be because these patients had a better chance of receiving a graft because of upgraded status.

In our experience, including adults and children, the presence of liver failure influenced patient survival rate.[22] However, in this selected series, it did not reach statistical significance ($P = .12$), maybe because of small sample size. None of the other factors reached statistical significance. There are trends toward better survival rates with transplantion in recent years ($P = .06$), greater body weight ($P = .084$), and waiting at home ($P = .14$). These facts suggest that the ideal pediatric candidate is one who is older with preserved liver function and is at home before transplant. The ideal timing for transplant is when the child has begun to exhaust intravenous access or has shown signs of liver dysfunction that still may be reversible with restored enteral nutrition. For patients without liver failure who underwent transplant at an age greater than 2 years, their survival rate reached 90% at 3 years. If patients can grow on TPN without liver failure, we should wait until they are older. These patients still should be assessed by the transplant center so as not to miss the appropriate timing for transplant. They may have additional benefit from waiting because bowel adaptation still may occur up to 36 to 48 months of age.[12-14]

There is another subset of patients who do not have the luxury of waiting. Liver failure seems to develop in these very early in life. In this study, 38% of recipients were less than one year old. Three quarters of them had concomitant liver failure. Typically, they are deeply jaundiced at presentation, with a huge spleen and a very enlarged firm liver. Some of them had evidence of portal hypertension and a history of gastrointestinal bleeding, most commonly from varices at the gastrostomy site. They are TPN intolerant and should be referred to a transplant center early. The patients who died on the waiting list are all in this category; most of them died of gastrointestinal bleeding.

The precise mechanism of TPN-related cholestasis is unknown. Several predictors for the development of this complication have been suggested by other investigators.[24,25] They include frequent bacterial infection, longer time with diverting ostomy, and low percentage of total calories taken enterally. Early cycling of TPN, meticulous catheter care, aggressive treatment of sepsis, and appropriate enteral feedings are recommended to prevent development of cholestasis.[24] However, despite these measures, a small portion of patients still have cholestatic liver disease.[25] These patients should be referred as soon as development of liver disease is realized. The results of this subset are not as good as in the former

group of patients, but they still have more than 50% one-year survival rate, and, in recent years, their results are improving. The body weight of the smallest patient who underwent transplant was 4.5 kg. We have performed transplants in 21 patients with body weights less than 8 kg. The results were poorer compared with patients with greater body weight but did not reach statistical difference. Intestinal transplant also should be considered in these small babies with liver failure, because they had no other way to survive.

In our experience, older age at transplant favorably influenced patient survival rate after bowel transplant. Stable patients on TPN should wait until they are older. However, babies who have cholestatic liver disease early in life should be referred to a transplant center as soon as possible.

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