Use of Split-Liver Allografts Does Not Impair Pediatric Recipient Growth

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The use of split-liver (SL) allografts continues to be an excellent option for many pediatric recipients. Patient and graft survival with this graft type are comparable to patient and graft survival with whole organ grafts. Quality-of-life issues, specifically growth, for SL recipients have not been compared to those of recipients of more conventional whole-organ recipients. Pediatric recipients of SL and whole allografts at 2 institutions were identified. Height, z score, and delta z score were calculated for all recipients for each year after transplant. Between 1995 and 2004, 201 pediatric liver transplants were analyzed. Data were collected on 39 split-graft recipients and 36 whole-size recipients. Only subjects 3 years or younger were included in the study. Growth retardation was present in all recipients at transplant. Height z score post split and whole-size transplant were not statistically different at 1- \( P = 0.65 \), 2- \( P = 0.13 \), and 3-year \( P = 0.32 \) anniversaries, respectively. Catch-up growth was present only in recipients of split grafts. In conclusion, the use of split grafts as opposed to whole-size grafts revealed no significant differences in terms of linear growth. Our report indicates that split-liver transplantation does not impair recipient growth. Liver Transpl 13:145-148, 2007. © 2006 AASLD.

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Split liver transplantation (SLT) was first performed in 1988. Since that time, numerous series have been published demonstrating the efficacy of this procedure in terms of survival advantage for pediatric recipients.¹-⁶ The SLT procedure generates a partial allograft, namely the left lateral segment, of a healthy adult liver that is transplanted into a child frequently weighing less than 10 pounds. It is well known that a healthy liver has an innate ability to hypertrophy and grow with time, and this ability has enabled the utility of this technical variant graft for children. The use of SL transplantation has significantly changed the ability of some transplant centers to offer timely transplantation to small children.⁷-⁸ The utility of this procedure in liver transplantation for children has not reached its full potential due to a number of policy, logistical, and ethical issues.⁹-¹¹

The vast majority of previous publications on SLT have focused on patient and graft survival as the primary endpoints in determining efficacy of the partial allograft. The results with SLT have been generally quite good across a broad series of patients in a number of different centers. The use of this procedure has been questioned in terms of its applicability relative to whole-organ and living donor liver transplants. Some previous publications with national data have demonstrated that inferior survival results are obtained with the use of SLT in comparison to living donor or whole-organ cadaveric transplantation.¹² Other series have shown equivalent results in terms of patient and allograft survival.¹,⁴,¹³ Limited information exists regarding clinical and developmental consequences of pediatric split-liver recipients in relation to whole-organ recipients. It is imperative that we continue to analyze the clinical aspects behind the use of partial allografts and its effect on the recipients. Most notably, pediatric patients continue to grow, albeit at different rates, before and after transplantation.¹⁴-¹⁶ Growth of pediatric liver transplant recipients is known to be altered in the presence of advanced liver disease. It is unknown whether growth and development are further impeded by the use of partial allografts.

PATIENTS AND METHODS

The records and growth data on pediatric recipients of split-liver grafts at 2 institutions (University of Texas...
Health Science Center in San Antonio-University Hospital, and Texas Children’s Hospital, Houston, TX) were retrospectively reviewed. The data were compared to those of pediatric recipients of whole-liver grafts. Because of the age group most likely to receive split grafts, the cohort included only recipients of age 3 or less.

Variables included in the study included: age at transplant, gender, diagnosis, waiting time on the United Network for Organ Sharing list, follow-up time, graft type, and rejection episodes. All of the grafts used were procured from deceased donors as a whole-size liver or as a split left lateral segment. Data on specific therapy for each rejection episode was not collected, and only biopsy-proven episodes were included for analysis.

The immunosuppressive regimen was similar for all patients and included (1) no induction therapy; (2) tacrolimus by mouth at a dose of 0.1-0.2 mg/kg/day with a target blood through level of 10-12 ng/mL (0-3 months posttransplant) and 6-8 ng/mL (4-12 months posttransplant); and (3) prednisone at a starting dose of 2 mg/kg/day with a taper goal of 0.1 mg/kg/day by 3 months, then discontinued after month 6-12 post-transplant.

Growth data included pretransplant height, as recorded on the admission for transplantation or less than 1 month prior to transplant, and height z scores for each individual patient, calculated with mean values and SD obtained from the Centers for Disease Control and Prevention 2000 United States growth charts.17 The following equation was used:

\[
\text{z-score} = \frac{(\text{Observed value} - \text{mean value})}{\text{Standard deviation of an age- and sex-matched population}}
\]

Height z scores were calculated at transplant and at each anniversary following the transplant. Growth retardation was present when the height z score was less than zero (0) SD. For example, a child with a height z score of −1.0 is 1 SD below the 50th percentile of an age- and sex-matched population and was considered growth retarded for the purpose of this study.

In addition, a delta height z score was calculated for each posttransplant year, with the following formula:

\[
\text{Height z score posttransplant year } X = \text{Height z score at transplant}.
\]

Catch-up growth was defined as a positive delta height z score and represents an upward trend of the growth curve for a particular recipient.

Statistical analysis was performed to detect interactions of all the variables with z scores. P values < 0.05 were considered statistically significant. Mixed Model ANOVA was run with SPSS software (SPSS, Inc., Chicago, IL), and height z scores were calculated with SAS software (SAS Institute, Inc., Cary, NC).

**RESULTS**

Between 1995 and 2004, a total of 201 pediatric liver transplants were performed at the 2 institutions involved in the study. Data was collected for 39 recipients of split grafts and 36 recipients of whole liver grafts who met the age criterion. Most patients were males (60%), and mean age at transplant was 1.13 ± 0.63 years. Mean waiting time on the United Network for Organ Sharing list for the cohort was 128 ± 147 days. The most common diagnosis for transplantation was biliary atresia (60%). Rejection episodes were present in 17% of cases. Patients were followed for a mean time of 5.05 ± 3.26 years. Detailed demographics of both groups are compared in Table 1.

Growth data was available for 90% of patients at or immediately before the time of transplant, 77% at 1 year, 53% at 2 years, and 42% at 3 years. Growth retardation was present among all recipients at the time of transplant; however, patients with fulminant failure had a z score closer to 0. The degree of growth retardation in patients with fulminant failure was significantly smaller only when compared to that of the patients under other diagnoses categories (P = 0.08). The z scores at time of transplant are shown in Table 2.

When comparing the linear growth of patients receiving split grafts as opposed to whole-size grafts, there was no significant difference at any of the first 3 post-transplant anniversaries (Table 3). Catch-up growth was analyzed during the first, second, and third consecutive posttransplant years. Only recipients of split grafts demonstrated catch-up growth in our study, but
not to a degree enough to be statistically significant (Table 4). In regard to etiology of liver disease, patients with a diagnosis of biliary atresia were compared to the rest of the group for each graft category. There was no significant difference in the catch-up growth of patients with biliary atresia when compared to other indications for liver transplantation ($P = 0.98$, 0.10, and 0.71 at posttransplant year 1, 2, and 3, respectively).

To determine any interaction of graft type and the variation of $z$ scores with other variables, a mixed-model ANOVA was performed. Factors such as gender ($P > 0.45$), diagnosis of biliary atresia ($P > 0.60$), waiting time ($P > 0.30$), and rejection episodes ($P > 0.40$) had minimal interaction with the differences in $z$ scores between the recipients of both types of graft.

**DISCUSSION**

It is well known that children suffering from chronic liver disease show delayed growth. Growth retardation is a manifestation of the higher incidence of malnutrition experienced by this group of patients. In children with liver dysfunction, factors such as anorexia, loss of taste, vomiting, and ascites lead to malabsorption, increased caloric demands, and inadequate oral intake. Without liver transplantation, many of these children continue with growth delay. The development of liver transplantation for small children has changed the prognosis of these patients during early development. Advances in immunosuppression have also increased long-term survival. The advent of new technical innovations, including living-related transplantation and SLT, have increased the options available to small children for liver transplantation. Improvement in long-term survival is coupled with an improvement in the quality of life and social aspects following liver transplantation. Growth following transplantation for children has been shown to increase substantially compared to that prior to transplantation. With the advent and utility of these technical variant grafts, little data has been presented in the literature in regard to their effect on the growth of the recipient.

In this study, we specifically chose a group of children under the age of 3 who had received either a split-liver graft or a whole-organ graft. In our experience, partial allografts are predominantly used for patients in that age category. At the same time, by excluding older recipients of whole-size grafts, factors such as catch-up growth can be compared more evenly among the study subjects. Pre-

### TABLE 2. The $Z$ Scores of Pediatric Transplant Recipients by Diagnostic Category

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
<th>$Z$ Score Pretransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>61</td>
<td>$-1.23 \pm 1.7$</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>19</td>
<td>$1.07 \pm 2.3$</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>10</td>
<td>$-0.32 \pm 0.6$</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>$-1.72 \pm 0.92$</td>
</tr>
</tbody>
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Vious reports have shown that, for recipients of a living related graft, the gain in height in the third year following transplantation is significantly higher in recipients of a living donor graft than in those of a whole-organ graft. In the literature, there is no reference to growth in relation to the use of SLT. In some aspects, the split-liver graft is comparable to a living donor graft, from an anatomical standpoint. However, from a functional standpoint, previous reports have indicated that SLT may result in inferior survival results for recipients of this type of graft compared to recipients of a living donor graft or a whole-organ graft. Other reports have shown comparable results in regard to survival with the split-liver graft vs. living related graft or whole-organ graft. Several studies have shown that the performance of the graft in terms of postoperative complications in the form of rejection, graft dysfunction, infection, and retransplantation are factors that affect catch-up growth in the long-term follow-up of these patients.

This study presents a unique comparison of recipients of a split-liver graft to those of a whole-organ graft. This comparison has not previously been reported in the literature to our knowledge. These groups would appear to be comparable in terms of demographic makeup and the etiology of liver disease. The height $z$ score after transplant up to 3 years does appear to be comparable between the recipients of split-liver grafts vs. recipients of whole-organ grafts. It is noteworthy that catch-up growth was consistently better in the recipients of a split-liver graft than in those of a whole-organ graft, even though statistical significance was not reached. The exact etiology and reason for this are unclear. A possible interaction of the growth factors involved with liver regeneration and the growth hormone/insulin growth factor axis could explain such a difference, and it deserves further study. What is apparent from these results is that in terms of growth, there is no obvious disadvantage for recipients of split-liver grafts vs. whole-organ grafts.

There are a number of limitations of this study that might include the nonstandardization of height measurements of recipients. Measurements obviously were not taken by the same person in the same environment for each recipient and were not available for all subjects at different time points. Another limitation would be the lack of detailed data concerning the use of steroids in recipients of these grafts. Long-term steroid use and dosage regimen are thought to be possible detriments to linear growth in the pediatric population. In this regard, rejection was analyzed as a surrogate marker for increased steroid exposure. However, rejection episodes did not significantly affect the differences observed in the height $z$ scores among the 2 groups. In addition, genetic factors such as the stature of parents of the recipients may likely play a role in the growth of the study subjects and was not taken into account.

In conclusion, these results show that liver transplantation does provide benefit to children, aged 3 years or less, in terms of linear growth relative to height prior to transplantation. The use of SLT does not appear to confer a posttransplant growth disadvantage in relation.
to the use of whole-organ transplantation. It is possible that SLT may confer some advantage in terms of catch-up growth over whole-organ transplantation. Due to the limitations of this study, these results should be validated by larger numbers in a well-controlled, multicenter database population.

REFERENCES


