Clinical outcome 10 years after infant heart transplantation

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Abstract

The feasibility of heart transplantation for infants has now been established. Clinical outcome data is necessary to assist in targeting areas for improvement and for counseling families considering this option. This report describes clinical outcome in 29 infant heart transplant recipients who have survived at least 10 years. A query of the transplant database, referring physicians and parental questionnaire was performed. Patient survival for the overall infant population is 64% at 13 years. Parents of 19/29 (55%) children described them as developmentally normal. Three children have had a severe developmental outcome. Sixteen of 29 children are in mainstream school environments. Four have repeated one grade in school. Speech delay was present in 10/26 (38%). Somatic growth is normal in 88%. All children are NYHA class I. Renal function shows only modest insufficiency with most recent BUN (mean ± S.D.) = 25 ± 7 mg/dl and serum creatinine = 0.8 ± 0.2 mg/dl. Only four children have creatinine levels > 1 mg/dl. No child requires dialysis. No children have developed post-transplant lymphoproliferative disease beyond 10 years. Four children have experienced rejection beyond 10 years with one mortality due to rejection and transplant coronary artery disease. Conclusion: Heart transplantation during infancy is technically feasible and results in good survival. Many children have some degree of learning disability but most are mild and the children function well in society. Improvements in surgical techniques may improve developmental outcome. Other side-effects of immunosuppression are manageable and most survivors have a good functional outcome. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The feasibility of heart transplantation for infants has now been established. Many technical issues related to donor and recipient management have become more routine. There is no longer a question as to whether this therapy can be applied to the youngest children. However, many health professionals do question the value of this procedure [1]. This issue is admittedly one with many ethical implications for families and society. In order to explore this issue, more information is required on the long-term outcome of infants who have undergone heart transplantation. This report is a descriptive analysis of children who underwent heart transplantation during infancy and who have survived at least 10 years.

2. Patient population

The pediatric allograft heart transplant program at Loma Linda began in 1985 with the successful transplantation of a 6-day-old boy who was born with hypoplastic left heart syndrome. Since that time 345 children (<18 years) have undergone 366 heart transplant procedures. Of these, 253 primary transplant procedures have been performed for children during the first year of life. Actuarial patient survival is
Actuarial Survival

Fig. 1. Actuarial survival of 253 infant (<12 months) heart transplant recipients. Numbers just above the x-axis represent remaining patients at each time point. Log rank comparison of newborns (1–30 days) to older infants (31–365 days) revealed a survival advantage for newborn recipients \( P = 0.0164 \).

illustrated in Fig. 1. Twenty-nine infants have survived at least 10 years with 322 patient-years of follow-up, including three who have undergone retransplantation. These 29 children comprise the population for this report.

3. Methods

Demographic and survival data were obtained from the pediatric heart transplant research database. Clinical outcome information was obtained via a structured telephone conversation with the parents of the children, by review of charts and by obtaining information from the follow-up physicians for those children no longer followed locally.

Specific information requested included current developmental status, school performance, requirement for speech therapy, activity level, growth parameters, renal function (blood urea nitrogen, creatinine and glomerular filtration rate where available) and rejection episodes beyond 10 years.

4. Results

4.1. Patient survival

Actuarial patient survival is illustrated in Fig. 1. Survival for the overall infant population is 68% at 10 years and 64% at 13 years. There is a survival advantage for transplantation during the first month of life. Newborn recipients \( n = 97 \) have a 77% actuarial survival at 10 and 13 years. This is in comparison to the remainder of the infants \( n = 156 \) who have 10- and 13-year actuarial survival rates of 62% and 52%, respectively \( P = 0.0164 \) by log rank test.

4.2. Developmental outcome

Parents were queried on the general developmental status as compared to their child’s peers. Nineteen of 29 (66%) described their child as being developmentally normal. Of the nine children described as abnormal, six consisted only of mild abnormalities of gross or fine motor control or difficulties in school.

Three children had significant developmental abnormalities. One child was normal until approximately 21 months after transplant when he suffered a severe rejection episode requiring ECMO support. Another child was developmentally normal until he suffered an episode of bacterial sepsis several months after transplantation. Both of these children have moderate to severe mental retardation and require full-time care. The third child developed autism.

Two children are being treated with psychostimulant medication for attention deficit hyperactivity disorder (ADHD) with good results.

Sixteen of 29 children (55%) are in full-time mainstream school settings. The remainder of the children
are in varying degrees of special education. Four have repeated one grade in school with two being able to return to mainstream classes.

Of the 26 children who do not have severe developmental delays, 10 (38%) have difficulty with speech. This is most commonly a mild difficulty in speech articulation. Two additional children, who are now described as normal, received speech therapy when they were younger.

Behavioral issues weren’t a concern for parents except for those children with ADHD or severe developmental delays.

4.3. Somatic growth

We have previously reported on somatic growth in the infant population [2]. Most children are in the normal range with most recent growth parameters (z-score; mean ± S.D.) showing a height of −0.48 ± 0.97 and weight of −0.55 ± 1.2. Most recent height was < 5th percentile in 12%. Risk factors for short stature included rejection history, degree of illness and especially parental height.

4.4. Activity level and graft function

All children, other than those with severe developmental delay, are described by their parents as having normal physical activity abilities. All would be classified as New York Heart Association (NYHA) class I.

Recent catheterization and echo data are available for a number of the children. Cardiac index by thermodilution and fractional shortening (for primary grafts only) were chosen as markers of cardiac function. Cardiac index (n = 14; in the absence of acute rejection) averaged 3.93 ± 0.97 1/min/m² with a range of 2.41–5.70 1/min/m². Fractional shortening (n = 10; again in the absence of acute rejection) averaged 36 ± 6% with a range of 25–45%.

4.5. Renal function

Renal function was assessed by measurement of blood urea nitrogen (BUN), serum creatinine and isotopic glomerular filtration rate (GFR) where available. Average BUN (n = 23) was 25 ± 7 mg/dl with a range of 10–42 mg/dl. Average creatinine (n = 24) was 0.8 ± 0.2 mg/dl with a range of 0.5–1.4 mg/dl. Only four children have serum creatinine levels in excess of 1.0 mg/dl. GFR averaged 77 ± 21 ml/min/1.73 m² with a range of 49–124 ml/min/1.73 m². Renal function studies have remained stable over time. We have had good success, even relatively late, by adding diltiazem for renal function protection. No child requires renal dialysis.

4.6. Post-transplant lymphoproliferative disease (PTLD)

No children have developed PTLD beyond 10 years after transplantation.

4.7. Graft rejection

Four children have experienced rejection beyond 10 years after transplantation. Three children have been successfully treated. One child succumbed to rejection 10.76 years after transplantation. On autopsy he had evidence of significant transplant coronary artery disease. One other child has angiographic evidence of mild transplant coronary artery disease that has been stable to slightly improved over the last two annual coronary angiogram studies.

5. Discussion

Clinical experience with infant heart transplantation has entered its second decade. Each year approximately 350 pediatric heart transplantation procedures are reported to the International Society of Heart and Lung Transplantation [3]. Of these, approximately one-third are performed for infants, with 74% having congenital heart disease as the primary indication for transplantation. Twelve-year actuarial survival in the infant population is approximately 43% and the conditional half-life (i.e. of those who survived the first year) is 13 years.

Many lessons have been learned and applied to the care of the infant heart transplant recipient. No longer is lethal heart disease in infancy a hopeless situation. Tempering this hope, however, is the realization that many lessons still need to be learned to improve the clinical outcome of these children. It is anticipated that improvements in surgical technique [4] and clinical management will make the lives of those infants transplanted now better than those transplanted a decade ago. Still, it is valuable to examine outcome data in order to inform us of important areas to concentrate our clinical attention and to give parents and health care providers improved data with which to make informed decisions.

A number of centers have presented outcome data [5–19]. Most of these reports have concentrated on mortality, rejection and infection. They conclude that pediatric heart transplantation is a viable option for children with lethal heart disease. Few reports, however, have commented on quality of life issues.

In a multicenter report [14] of 68 children who have survived at least 5 years, the longest reported surviving pediatric patient was 17.9 years post-transplant. Systolic function was normal in most allografts. Fifteen had attended college. Persistence of height below
the fifth percentile was observed in 16 patients. All survivors were in NYHA class I at latest follow-up.

Parisi et al., in a recent report [19] of 10-year follow-up from Ospedale Bambino Gesù in Rome, Italy, reported 11-year actuarial survival of 42%. Of 36 survivors, 32 were reported to have normal growth, development and neurologic outcome. All of them had returned to normal activities for their ages, including school and sports.

Webber from the University of Pittsburgh, in a discussion of their 15 years of experience with pediatric heart transplantation [15], reported that normal physical activity could be resumed in all recipients. He also commented on the concern that many recipients have difficulty adjusting to life after transplantation, especially during adolescence. The infant recipients in our report are just now entering adolescence and we have yet to see whether they will have this same difficulty. It is likely, however, that they will cope better since transplantation is all they have known, unlike the child who had normal cardiac function until later in life.

Gajarski et al. from Texas Children’s Hospital noted [18] that, though no formal evaluation for quality of life was performed, all patients had good to excellent functional status after transplant (NYHA class I).

Several reports have commented on late renal function. In the multicenter report [14], renal function, assessed by serum creatinine levels, was abnormal in 54% of survivors and two patients had undergone successful renal transplantation 5 and 7 years after heart transplantation. Radley-Smith and Yacoub from Harefield Hospital in the UK noted a tendency of creatinine levels to rise over time. No child, however, had been taken off cyclosporine due to deteriorating renal function. And, using a non-steroid-based immunosuppression protocol, the only child who required antihypertensive therapy was a child with pheochromocytoma. This is similar to our experience.

Serial GFRs in our population have been relatively stable over time. As noted above, when we see a deterioration of renal function we have had good success with verapamil or diltiazem. Both of these calcium channel blockers compete with cyclosporine for metabolism, allowing lower cyclosporine dosing. In addition, they counteract the vasoconstricting properties of cyclosporine.

Graft rejection is possible even late after infant transplantation. Most of this, in our experience, seems related to issues of compliance though this is hard to quantify. It does, however, emphasize the need for continued vigilance in the screening process for rejection.

We have previously reported on developmental outcome early after infant heart transplantation [20]. This report extends this information to those children who have survived at least 10 years after transplantation. It is limited by the subjective nature of the data collection. We are in the finishing stages of a much more formal evaluation of neurodevelopmental outcome in recipients of infant heart transplantation who are now of school age. In the current report, three children (10%) have had serious neurologic sequelae. Two were apparently normal until severe rejection and infection occurred. It is unclear whether the autism affecting the third child is related to transplantation, since there are other psychiatric diagnoses in the family. An additional 35% of the children have some degree of learning disability requiring special educational resources. An additional finding is that 38% have received or are receiving speech therapy. Most are easily understandable by the time they are 8–10 years old.

These neurodevelopmental findings are not dissimilar from other populations of children with chronic medical conditions or who are neonatal intensive care graduates. Our early developmental outcome data are similar to results for infants who have undergone staged surgical repair for hypoplastic left heart syndrome [21]. We believe that improvements in the circulatory arrest protocol and in surgical techniques (see Del Rio, this review) that decrease the circulatory arrest time should be less harmful.

6. Conclusion

Ten-year follow-up data is now available for a significant number of infant heart transplant recipients. This report, however, should not be interpreted as representing current potential but rather as a report of what has been achieved and what should be expected as a minimum benchmark for further studies. Ten-year survival in this population, while valuable, is a tantalizing prelude to what is hoped will be a much longer life span. In order to reach 10-year survival, 10% of this population has undergone a second heart transplant. A more complete discussion of transplant coronary artery disease (TCAD) is available elsewhere in this monograph. But, TCAD is the limiting factor to long-term survival. Quality of life issues are extremely important and need more thorough evaluation and follow-up. While many of these children have mild to moderate learning disabilities, they enjoy a good quality of life and can enjoy the usual activities that bring joy to children and their families.

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References