Paediatric cardiac transplantation

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Abstract
Paediatric heart transplantation has become firmly established as a treatment modality for end-stage heart failure due to either cardiomyopathy or congenital heart disease. Numbers of transplants are limited by donor numbers and therefore there has been an impetus for the development of mechanical support which may allow patients to wait for a suitable organ. It is important for all professionals involved in the care of the post-transplant patient to be aware of potential complications and the ever-present possibility of graft rejection in order to provide the highest standard of care. Practice has evolved over the decades and increasing experience along with the development of immunosuppressive agents and improved post-operative care has led to an improvement in survival figures and outcomes.

Keywords cardiac; paediatric; transplant

Introduction

The first paediatric cardiac transplant by Adrian Kantrowitz in New York in December 1967 occurred just three days after Christiaan Barnard's milestone first adult transplant in Cape Town. Kantrowitz transplanted the heart of a baby with anencephaly into a 3-week old neonate with a clinical diagnosis of tricuspid atresia and although initially the procedure appeared to have gone well, the patient went into cardiac arrest and died after six hours.

Over subsequent years there were numerous further attempts but outcomes remained poor until the breakthrough discovery of Ciclosporin in 1976. Survival has increased dramatically since then with research and practice from the 1980's focused on the introduction of newer drugs for immunosuppression, patient selection, addressing long-term issues in survivors and ethical challenges. Furthermore, significant progress has been made in the field of mechanical cardiac support as a bridge to transplant (or even to recovery of heart function) with extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). Newer challenges include attempts at inducing graft tolerance, transplanting higher risk patients including those with pre-formed human leukocyte (HLA) antibodies and stem cell therapy. The decline in donor availability remains a limiting factor for all transplant programmes and waiting list mortality is still significant.

Each year, approximately 400–500 paediatric cardiac transplants are performed worldwide and encouragingly, outcomes continue to improve with many of these patients surviving into adult life and more than 50% of patients now alive 15 years after transplant. In the United Kingdom, 30–40 transplants are carried out per year between the two cardiac transplant centres for children, the Freeman Hospital in Newcastle upon Tyne and Great Ormond Street Hospital in London.

Indications for transplant

Most children assessed for cardiac transplantation have either complex congenital heart disease (CHD) or primary heart muscle disease (cardiomyopathy). Approximately 25% of all paediatric heart transplants worldwide are carried out in infancy with a slight predominance of patients with congenital heart disease (mainly single ventricle physiology and more complex malformations) in this group. This is in contrast to older children and adolescents in whom cardiomyopathy is by far the most prevalent indication for transplant (approximately two thirds of patients).

Primary cardiac transplantation for neonates with hypoplastic left heart syndrome has been carried out with survival rates above 80% in some centres but the majority of these patients now undergo an attempt at palliative surgery. This is both due to the improving results of surgical palliation and the shortage of donor organs for smaller infants. As survival with congenital cardiovascular malformations improves, we may see more children with these conditions requiring transplantation in adolescence or young adulthood for later onset heart failure. An important subgroup is patients who have undergone previous Fontan procedures for single ventricle palliation or following cavopulmonary shunts. These patients may have additional comorbidities such as protein-losing enteropathy, pulmonary arteriovenous malformations, liver cirrhosis and other sequelae of their failing Fontan circulation causing transplantation to be of increased risk.

The majority of patients with congenital heart disease will have undergone previous surgical palliation and technical surgical factors around the time of transplantation need consideration. There may be abnormalities in the great vessels or the heart may be in an unusual position in the chest, as in cases of dextrocardia. In order to compensate for and correct these problems, surgeons carrying out retrieval of the donor organs need to obtain additional tissue such as extra length of the vena cavae and this needs to be planned for in advance. Many of these patients have also had previous blood transfusions or surgical interventions involving immunogenic tissue (such as homograft conduits) and have developed pre-formed HLA antibodies making it more difficult to find suitable donors.

Although often idiopathic, there may be a number of causes of dilated cardiomyopathy and a full metabolic and genetic screen looking for underlying pathology is routinely performed at the time of presentation in heart failure. Mitochondrial disorders

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need to be excluded if possible but inevitably these may sometimes only be diagnosed following transplant on examination of frozen sections of the explanted heart. A small percentage of patients have cardiomyopathy secondary to anthracycline-containing chemotherapy for conditions such as childhood leukaemia. Other forms of cardiomyopathy such as hypertrophic cardiomyopathy and restrictive cardiomyopathy are less common indications for transplant.

Children in heart failure often present acutely unwell and in these cases it is difficult to differentiate between cardiomyopathy and myocarditis, which in some patients would be expected to recover. Intensive care support and mechanical assistance may be indicated, following a twin track approach of bridge to transplant or bridge to recovery. Transplant assessment should be carried out early in selected patients.

Assessment for transplantation

Children are referred for transplant assessment either due to cardiac failure of any cause with the prediction of poor longer-term survival (usually accepted as a life expectancy of less than one year) or poor quality of life. The decision to list for transplantation usually incorporates a complex assessment process involving a multidisciplinary team of cardiologists, surgeons, transplant co-ordinators, nursing staff, psychologists and social workers. The pros and cons of transplantation are discussed and any alternative management options such as further palliative or corrective surgical options carefully considered. Increasingly, children are transferred in severe cardiac failure on maximal inotropic support and then there is the immediate need for consideration of bridging with mechanical support to recovery or transplantation if this is appropriate.

The list of absolute contraindications to transplant has decreased over the years and the main one is now ongoing malignancy. There are very few anatomical reasons why transplantation may not be possible. Pulmonary vascular disease, pulmonary vein stenosis or abnormalities of the pulmonary arterial tree may however preclude heart transplantation alone and these patients may need consideration for heart-lung transplantation.

Transplantation in the face of chronic viral infections such as hepatitis B or C and HIV remains controversial and there is little experience in the paediatric population. Genetic and chromosomal conditions such as Down's syndrome are usually not a bar to transplant but the decision depends on the assessment of associated co-morbidities. Similarly, neuromuscular conditions with mainly cardiac involvement are not in themselves a contraindication to transplantation although careful counselling of families is needed prior to listing.

Waiting for transplant and mechanical support

Waiting times for transplant vary widely depending on the age and size of the patient, blood group and the presence of pre-formed HLA antibodies that may need to be avoided when considering potential donors. There is now increasing data on the impact of these pre-formed antibodies and on the development of *de novo* donor-specific antibodies post-transplant, with evidence that these antibodies may play a role in long-term graft outcomes.

Size-mismatching is commonly practiced, with donor hearts up to three times bigger than recipients (based on body weight) utilised. Traditionally it has been necessary to match the donor-recipient blood groups to prevent rejection but work from Toronto in the late 1990s demonstrated that ABO blood group incompatible transplantation is possible in infants and young children with relatively immature immune systems and low blood group antibody titres. Outcomes in this group are comparable to ABO-compatible transplants and this practice is now widely carried out in Canada and the United Kingdom and has led to a reduction in waiting list mortality.

Although the risk of death while waiting for transplant has progressively decreased, it remains significant especially in the infant group. Analyses of the Pediatric Heart Transplant Study group registry in the United States have shown an overall waitlist mortality of 11% at one year but improved survival over time which may also be related to improved intensive care and the introduction of mechanical support. Children in heart failure may require intravenous inotropic support with drugs such as dobutamine and milrinone and some need positive pressure mechanical ventilation in order to achieve an adequate cardiac output. In those in whom this is insufficient, mechanical support (in the form of ECMO or increasingly VADs) may be used. ECMO is essentially a form of cardiopulmonary bypass and is the support of choice in the emergency or arrest situation as it can be deployed relatively quickly. This can be used for limited time periods as complications such as infection, bleeding and clot formation in the circuit rise exponentially after 2 weeks and studies have shown that the overall chance of survival to hospital discharge while listed on ECMO is only around 50%. Therefore alternative means of providing longer-term support have been developed and there are now a number of ventricular assist devices (VADs), which can provide support to either the left or both ventricles. The most commonly used device in small children and infants is the Berlin Heart Excor® VAD which can be used as a support to either transplant or recovery. Patients with this device have a high risk of clot formation, with approximately a third suffering strokes, and therefore they require meticulous care with anticoagulation and are generally confined to a hospital setting. More recently, there is increasing experience with adult-type VADs such as the Heartware® H Ventricular Assist System which may be more appropriate for long-term support in adolescents but there is increasing evidence that it may be effective in younger children and may enable patients to go home on support while awaiting transplant.

Transplant surgery and care following transplant

The heart is usually part of a multiorgan procurement and is the last organ to be removed. Once it is determined that the heart is suitable, the recipient is moved to theatre and initial chest opening and dissection done before the donor organ arrives in order to minimise the amount of time for which the heart is ischaemic. The most commonly used implantation technique is the bicaval anastomosis in which the superior and inferior vena cavae and the aorta and pulmonary artery are joined directly and pulmonary veins anastomosed to the donor atrium on a flap of recipient atrium.

Initial post-transplant management includes intensive care strategies to ensure optimal haemodynamics, monitoring of titres