Pediatric Heart Transplantation in Refractory Cardiogenic Shock: a Critical Analysis of Feasibility, Applicability and Results

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Summary

Background: In children with dilated cardiomyopathy who are on the waiting list for heart transplantation, we evaluate the seriousness of their hemodynamic conditions. Some develop cardiogenic shock, and the mortality rate is high. Even with inotropic and respiratory support, heart transplantation is considered an extremely grave circumstance.

Objective: The objective of this study is to report on our experience with children in this condition, in an attempt to analyze the viability, applicability and results of heart transplantation in these children.

Methods: From March 2001 to February 2004, 22 children with dilated cardiomyopathy who were on the waiting list for heart transplantation developed cardiogenic shock, requiring transfer to pediatric intensive care unit (ICU), intubation and inotropic support. Their ages ranged from 11 months to 11 years (mean age: 4.3 years), 55% were males, 14 could be listed as clinical priority, and the remaining 8 were removed from the waiting list due to their unfavorable clinical conditions.

Results: Eight heart transplantations were performed, and 6 children died while on the waiting list (42.9%). Two children died (25%) after transplantation and the remaining 6 were discharged from hospital in good clinical condition. The two main complications were organ rejection in 4 cases and infection in 5 cases. Two patients developed neurological complications, and one of them fully recovered.

Conclusion: Children with cardiomyopathy and cardiogenic shock require immediate heart transplantation; only 57.1% could be transplanted, with an early 25% mortality rate. Those who survived transplantation showed good clinical progress, similar to that of children transplanted on an elective basis. (Arq Bras Cardiol 2008; 90(5): 329-333)

Key words: Heart transplantation; child; shock, cardiogenic.

Introduction

Among patients with cardiomyopathies of different etiologies who need to undergo heart transplantation, pediatric patients are those least likely to obtain organs in a timely fashion, especially due to their lower body weight and the reduced availability of compatible donors. The prognosis for pediatric patients listed for heart transplantation is guarded and short-term mortality while awaiting a compatible organ may reach 20%, and even 31% for children under 6 months of age[1-5].

In the progression of cardiomyopathic children, rapid clinical deterioration with possible development of hemodynamic decompensation and even cardiogenic shock are troubling events that require immediate therapeutic measures, such as the use of vasoactive drugs, mechanical ventilation and dialysis; in some cases, these measures are not enough to prevent imminent fatal outcomes[5,6]. When this is the case, heart transplantation is a salvage measure and the search for organs must be a priority for this group of patients.

Other clinical measures, such as the use of mechanical circulatory support devices, especially extracorporeal membrane oxygenation, have proven effective for patients in cardiogenic shock, serving as a bridge to heart transplantation or, less often, to the recovery of cardiac function[7-10]. Surgical alternatives to heart transplants have a high rate of mortality and complications, especially when performed on an emergency basis[11].

The aim of this study is to report on the experience with pediatric patients in cardiogenic shock at our institution, and to assess the feasibility, applicability and results of heart transplantation as the therapeutic measure to be adopted for this severely ill group of patients.

Methods

At the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*, pediatric patients with cardiomyopathies of different etiologies were evaluated who developed hemodynamic deterioration and even cardiogenic shock.

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Cardiogenic shock was considered in any patient requiring admission to the ICU, continuous use of two or more endovenous vasoactive drugs for more than 48 hours, besides orotracheal intubation and mechanical ventilation. The presence of renal failure whether or not requiring dialysis and other signs of low cardiac output, such as ventricular arrhythmias and hepatic failure, were also signs taken into consideration, although not exhibited by all children. Renal failure is defined as the clinical situation in which there is a reduction in diuresis volume to levels below 1 ml/kg/hour during the use of loop diuretic agents (furosemide) for at least 12 hours, in addition to increased serum urea and creatinine levels to 100mg/dl and 1.5 mg/dl, respectively.

From March 2001 to February 2004, 22 children, aged 11 months to 11 years old (mean age 4.3 years), 12 (55%) of which were males, displayed criteria for cardiogenic shock. Among these 22 children, 16 (73%) had idiopathic dilated cardiomyopathy, and 6 (27%) had a diagnosis of cardiomyopathy associated with congenital heart disease, 3 of them had already undergone cardiac surgery and 3 of them with no prior surgery. The different congenital heart disease diagnoses and the presence of prior surgical procedures are shown on Table 1.

The transthoracic echocardiogram showed a significant depression of left ventricular function with delta D values ranging from 6% to 18% (mean 10.2%). Dialytic renal failure was detected and treated by peritoneal dialysis in 9 (41%) patients.

Of the 22 patients, 6 had undergone previous operations. Table 2 displays all surgical procedures previously performed.

Only 14 (63.6%) patients could be enrolled on the priority list for heart transplantation. Of the 8 other children, 6 had contraindications for the procedure and two of them died even before being placed on the waiting list, less than 24 hours after onset of the cardiogenic shock. As to the contraindications for the procedure, 4 were clinical and 2 were of a social nature. Table 3 displays the different diagnoses, ages and reasons for contraindications.

Of the 8 children not on the list for heart transplantation, 7 (87.5%) died within 7 days after the decision was made to not subject them to the procedure. One infant with an unexplained genetic syndrome returned to the institution of origin, and no further information was obtained as to his/her clinical progression.

For the last case of the series, due to the patient's clinical and hemodynamic deterioration, extracorporeal membrane oxygenation (ECMO) was employed as a bridge to heart transplantation using the mechanical circulatory assist modality. The circuit consisted of a centrifugal pump, conventional membrane oxygenator for extracorporeal circulation (OXIM – Edwards), besides tubes, connectors and heat exchanger. Cannulation of the right atrium and aorta was performed in the operating room, through median thorocotomy. The cannulas were exteriorized through an opening opposite the surgical wound; at the time of implantation of the assist device, no appropriate cannulas were available to implant the device without having to open the chest, through femoral or cervical approaches. The patient was a 9-year-old girl with idiopathic dilated cardiomyopathy, delta D 6% and shock refractory to the use of optimized doses of dobutamine, dopamine and noradrenaline. After being placed on the priority list for heart transplant, she suffered a cardiac arrest which was reversed within 5 minutes. The employment of an extracorporeal membrane oxygenator was then indicated. The condition was so severe that between the preparation of the material and the beginning of the procedure, which lasted approximately 2 hours, the patient suffered a new cardiac arrest. After use of the mechanical

Table 1 - Patients with cardiomyopathy of congenital etiology

Patient	Age	Diagnosis	Previous surgery
IET	11 years	Tricuspid atresia IIIA	Yes
FFF	1 year	Interventricular communication +Interatrial communication+ Valvular-infundibular pulmonary stenosis +Hypoplasia of the left ventricle +Hypertrophy and dysfunction of the right ventricle	No
LSS	3 years	Interatrial communication +Pulmonary valve stenosis +Pulmonary failure	No
VSP	1 year and 9 months	Interventricular communication +Pulmonary hypertension	No
MELL	1 year and 7 months	Interventricular communication+ Myocarditis	Yes

Table 2 - Surgeries performed previously to the cardiac transplantation

Patient	Age	Diagnosis	Previous surgery
RRS	3 years	Interventricular communication +Total postoperative atrioventricular block	1.Ventricular septoplasty 2.Permanent pacemaker implant
IET	11 years	Tricuspid atresia IIIA	1. Blalock-Taussig operation+Pulmonary trunk bandage 2.Glenn operation + Atrioventricular valvoplasty
MELL	1 year and 7 months	Interventricular communication+Myocarditis	Ventricular septoplasty
JVM	1 year and 4 months	Cardiomyopathy	Ligature of the thoracic duct
BML	1 year 1 month	Cardiomyopathy +Total atrioventricular block post endomyocardial biopsy	Permanent pacemaker implant
AA	9 years	Cardiomyopathy	Implant of extracorporeal membrane oxygenation

Table 3 - Patients non on the list for cardiac transplant

Patient	Age	Diagnosis	Contraindication
TABN	2 years	Cardiomyopathy	Pulmonary hypertension
LSF	1 year and 1 month	Cardiomyopathy	Genetic syndrome
PCB	4 years	Cardiomyopathy	Social
LSS	3 years	Underlying heart disease (%)	Neurological abnormality
TSMV	6 years	Cardiomyopathy	Social
VSP	1 year and 9 months	Underlying heart disease (%)	Pulmonary hypertension
GRC	3 days	Cardiomyopathy	Death
MELL	1 year and 7 months	Underlying heart disease (%)	Death

circulatory support, the patient stabilized and she was able to await a compatible organ.

Bicaval orthotopic cardiac transplantation was the surgical technique employed in all cases, and Roe's solution was used for donor heart preservation. All donor hearts came from distant locations within the state of São Paulo. The postoperative immunosuppression consisted of a double combination regime (azatioprin + cyclosporin) with corticoids during the first 48 hours and antithymocyte serum during the first week. Anti-rejection therapy consisted of clinical measures and noninvasive tests (echocardiogram and Gallium scintigraphy); endomyocardial biopsy was performed for those cases of rejection difficult to manage or cases with a doubtful diagnosis[12,13].

Results

Eight children (57.1%) were transplanted, 50% of whom were females, and the age for both genders ranged from 1 to 11 years (mean age: 5 years). Recipient mean body weight was 13.4 g (7 to 22 Kg), whereas donor mean body weight was 38.4 Kg. Of the transplanted patients, 4 (50%) had suffered at least one episode of cardiac arrest. Among the patients, the most common blood type was O^+ (62%), and their delta D was, on average, 9% (6 to 12%). The time on the waiting list for a compatible organ ranged from 3 to 33 days (mean: 14.1 days). The child who had a mechanical circulatory support device implanted as a bridge to heart transplant underwent transplantation 3 days after being placed on the priority list.

Waiting list mortality was 42.9% (6 patients), on average 25 days after being placed on the priority list. Of the patients who died while waiting for an organ, 5 had idiopathic dilated cardiomyopathy and their delta D ranged from 6 to 16 % (mean: 10.5%). The most common blood type in this subgroup was O^+ (66%). Ages ranged from 11 months and 3.5 years (mean: 18 months).

All patients with idiopathic dilated cardiomyopathy who underwent heart transplantation survived the procedure and, despite the difficult initial clinical progress phase, their renal and cardiac functions recovered and they were discharged from the intensive care unit, on average, on postoperative day 27 (postoperative days 11 to 45).

Hospital mortality after cardiac transplantation was 25%, observed in the two patients with diagnosed congenital heart disease. One of them had a cardiac arrest during induction of anesthesia, and died on postoperative day 20, whereas the other patient developed graft rejection and died on postoperative day 40.

Infection was the most common early complication (5 cases). Acute rejection was observed in 4 patients, whereas 2 patients had neurological complications. One of them had a convulsion on the postoperative day 13, but fully regained neurological functions with no sequelae; the other patient had a cerebrovascular accident with left-side motor sequelae, during the progressive recovery phase.

Three patients needed to undergo reoperation surgery, 2 of them requiring elective pericardial drainage due to a major effusion, whereas the other one needed to have a surgical ligature of the thoracic duct due to a difficult to treat chylothorax.

Postoperative follow-up lasted from 1 to 32 months (mean: 18.6 months), and one case of late mortality was recorded in a patient who had been hospitalized to treat a rejection episode 1 year after heart transplantation. The other children are being followed as outpatients and are receiving immunosuppression treatment as mentioned above. They are asymptomatic from a cardiovascular point of view, with clinical progress profiles similar to those of children transplanted on an elective basis.

Discussion

Among the medical groups who perform heart transplants, especially in the pediatric population, the possibility of obtaining an organ within a short period of time for children with cardiogenic shock is one of the most vital concerns. In developed countries that already have consolidated transplant programs, the average waiting time for a heart, for a *status 1* patient (UNOS), is 53 days[14].

Besides the aspects of harvesting structures, which differ greatly among different regions of the country, another factor to be considered is the difficulty to find body weight compatibility between donors and recipients, as this pediatric population is usually under 30 kg of weight.

In our group of patients, the mean body weight was approximately 30% of that of the donors, which illustrates the problem and the difficulty to obtain donors that are more compatible. One aspect that minimizes this difficulty is the fact that most of the transplanted children had Idiopathic Dilated Cardiomyopathy, with enlarged cardiac areas, which enabled compatibility between the recipient and the size of the implanted heart.

Donor shortage, especially in the pediatric population, reflects a worldwide concern with reducing mortality on the waiting list; the progressive advances in this aspect refer to circulatory support devices as bridges to cardiac transplant, which are increasingly more widely used and divulged[1-

[3,6,7,10,15]. In our experience with this group of recipients, extracorporeal membrane oxygenation, which is still in its initial phase of utilization, was used in only one child with highly satisfactory results, good recovery and progression after heart transplantation, besides the short waiting time (3 days). Despite being just one case, we do believe that there is a great applicability potential for extracorporeal membrane oxygenation and other devices in the pediatric population, as an attempt to reduce the existing gap between donor pool and the increasing demand for donor hearts.

The high incidence of patients (8 patients - 36%) in our group who could not be placed on the waiting list due to contraindications for heart transplantation reflects two things. First, the delay in referring these patients to the heart transplant center which worsened their condition even further and wasted precious time for their survival. Previous studies corroborate the fact that *status 1* patients (UNOS)[14], that is, those who are taking maximum doses of vasoactive drugs, must be rapidly referred to pediatric transplant centers. This would reduce the incidence of infection among these patients and dysfunction of multiple organs at the moment of transfer, thus increasing the chances for a successful heart transplantation[1,2]. Another point of evidence is the high rate of social contraindications within our environment. Even with a trained multidisciplinary team, in some cases the precarious social and family structures limit use of the procedure.

In our group of patients, a more guarded prognosis was observed relative to those patients with congenital heart disease who were on the priority list, as described in a significant part of medical literature[16], despite the fact that some studies do not show a significant difference between patients with idiopathic dilated cardiomyopathy and those with congenital heart disease[1].

Extracorporeal membrane oxygenation has increasingly gained popularity in the treatment of this specific group of patients, with promising results that have brought hospital mortality down to 11%[2,9,10,17,18]. Additionally, long-term results also support the use of this type of device[17,19,20].

The Implantable Artificial Ventricle[21] and the Intra-Aortic Balloon[8] have also shown satisfactory results; however, despite being used for the adult population, their use in children is difficult due to the unavailability, in our country, of devices of an appropriate size for the height and weight of these patients.

Cardiac transplantation still has many obstacles to overcome. For children on the priority waiting list the challenges are huge. A patient in cardiogenic shock in a pediatric intensive care unit has a guarded prognosis for survival if the natural course of the disease overrides the therapeutic efforts currently available. The use of circulatory support devices combined with optimized vasoactive drugs has proven useful during the bridge to transplant.

Another important aspect that should be emphasized is the need to maintain the efforts to keep the population educated about organ donation. This should be seen as a fundamental part of the whole process so that pediatric patients can be treated in a timely manner. Nevertheless, social aspects offer significant barriers that must be faced in order to eradicate contraindications of this nature.

We believe that research in the management of pediatric patients requiring cardiac transplantation who are in shock has ample room for new studies to be undertaken, especially as to circulatory support devices as bridges to definitive treatment.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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