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RESEARCH ARTICLE

Ten-year experience of pediatric heart transplants: Hospital Infantil de México Federico Gómez

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ABSTRACT

Background. Hospital Infantil de México Federico Gómez (HIMFG) (National Institute of Health, Mexico) is recognized as a referral center for pediatric solid organ transplants nationwide. The first heart transplant was carried out in the institution on June 21, 2001, thereby establishing a program for pediatric heart transplant for the first time in Mexico. We present the results of a 10-year period.
Methods. We carried out a descriptive study including all patients undergoing heart transplantation at the HIMFG from 2001 to 2011.
Results. There were 23 heart transplants performed in our hospital with 11 females and 12 males. The most frequent indication for transplantation was dilated cardiomyopathy. Currently, we have a 50% survival rate with an improvement in survival each year during the past 5 years. At 10 years of heart transplantation in our unit, we found a significant difference between survival of patients with congenital heart disease vs. dilated cardiomyopathy. Significant differences were also shown in regard to complications.
Conclusions. Pediatric heart transplantation has evolved into a therapeutic option for complex congenital heart disease and end-stage cardiomyopathy.

Key words: heart, transplantation, pediatrics.

INTRODUCTION

Hospital Infantil de México Federico Gómez (HIMFG), a health institute recognized as a referral center for pediatric solid organ transplants nationwide, carried out the first heart transplant in the institution on June 21, 2001. The pediatric heart transplant program, for the first time in the country, included patients ranging from newborns to teenagers, offering new expectations in the management of severe heart diseases that were previously untreatable.[1] Similarly, heart transplants have changed the relationship between cardiology teams and pediatric practice and teaching because it requires close collaboration between groups in order to obtain good results based on knowledge of disease process, procedures and possible complications.[2] This allows appropriate decision making about the care and management of patients, either hospitalized or in the community and before or after receiving a graft. This paper aims to present the experience at the HIMFG as the first institution with a pediatric heart transplant program in order to improve program limitations and patient monitoring as well as to motivate other institutions to refer their candidate patients and/or promote programs of pre- or post-transplant care in other institutions.

The first successful pediatric transplants were performed at Stanford Hospital in 1970, but the initial enthusiasm decreased with problems of rejection.[3-7] In 1980, the immunosuppressive properties of cyclosporine were applied clinically and, in 1986, Leonard Bailey reported the first successful series heart transplantation in neonates with hypoplastic left ventricular syndrome at the University of Loma Linda, California.[8-11]

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PATIENTS AND METHODS

We conducted a descriptive, observational, longitudinal, retrospective study in the HIMFG in cardiac transplant patients from 2001 to 2011.

We included all patients in the HIMFG with a diagnosis of terminal heart disease. Most of the patients were outpatients prior to the transplant being treated with anticongestive medications. Hospitalized patients (two patients) were under inotropic support with levosimendan.

We excluded patients who did not fulfill the requirements established by the Department of Social Work, those with incomplete clinical analysis or those lost to follow-up by the hospital, as well as patients with incomplete clinical records. Limitations of the study consisted of the difficulties of following patients in the long term as well as patients who abandoned treatment.

Statistical analysis

Frequencies and percentages of normally distributed qualitative variables (average and standard deviation) and non-normally distributed variables (median and interquartile intervals) were calculated.

Demographic aspects

As of June 21, 2001 and to date, there were 23 heart transplants performed in the HIMFG. Of these patients, 11 were female and 12 male, with a mean age of 7 years (mean age for females was 3 years and for males was 8 years). Mean weight was 21 kg. The lowest weight for a patient was 4 kg. Indication for cardiac transplantation was congenital heart disease in 11 patients and cardiomyopathy (80% idiopathic dilated cardiomyopathy and 20% familial cardiomyopathy) in 12 patients.

Blood type frequency for patients was O positive (O+) in 82%, A positive (A+) in 9% and B positive (B+) in 9%; 13% had renal insufficiency prior to the transplant as well as malnutrition in 41%. Patients remained on the waiting list an average of 1 year 2 months.

Preoperative

According to the transplant protocol, all patients had serological tests performed. Two patients were positive for cytomegalovirus (CMV) (9%), one patient was positive for toxoplasmosis (4.5%), one patient was positive for Epstein-Barr virus (EBV) (4.5%), 13% of patients were positive for hepatitis A, and one patient was positive for herpes (4.5%). Patients were negative for HIV and VDRL. The percentage of ambulatory patients before transplantation was 80%. The remaining 20% were hospitalized patients without inotropic support. The mean pre-transplant hospital stay was 24 days. Twenty-three percent of the patients had nosocomial infection prior to transplantation, which was treated with broad-spectrum antibiotics.

Donor

As for the donors, 63% were males (14 donors) and 36% females (eight donors). The mean age was 7 years 3 months and mean weight was 25.5 kg. The host/donor relationship ratio never exceeded 1/1.5 in all patients. Causes of death of the donor were head injury (50%), intracranial hemorrhage (18%), gunshot wound, hypoxic-ischemic encephalopathy, drowning, congenital hydrocephalus and brain tumors (13%). Blood type was the same between the donor and recipient in 95.5%. Only 4.5% were incompatible with blood group (O+/A+ in one patient). The donor serology was positive in 13% for CMV (two IgG positive, one IgM positive). Hepatitis, VDRL and HIV were negative in all donors. Antivirals such as ganciclovir were initiated in these patients during the immediate postoperative period, as indicated by the International Society for Heart and Lung Transplantation (ISHLT) guidelines.[12]

Intraoperative

Donor heart extraction is performed through a median sternotomy with bypass of blood to the heart via left and right atriotomies, aortic clamping and infusion of hypothermic crystalloid cardioplegia. According to the general rule in pediatrics (and especially when the recipient has congenital heart disease) the innominate vein, the aortic arch and both branches of the pulmonary artery should be included in the donor heart block for the reconstruction of these structures. The graft is placed in sterile bags with saline at 4°C and transported into the thermal container. This is done in 100% of our grafts.

Surgical time had a median of 5 h. Ischemic time had a median of 4 h (none exceeded 6 h of ischemia). Infusion time had a median of 3 h.[13-15]

Postoperative

During postoperative management, all patients required aminergic support with dopamine, dobutamine, and iso-

proterenol. Patients remained on assisted mechanical ventilation with a mean of 1 day. The hospital stay in surgical therapy had an average of 5 days. We performed biopsies 1 month after transplant. If the recipient was very small, control echocardiograms were performed without biopsy unless there was a demonstrated risk of rejection. In adolescents, we performed biopsies (at least three) at 6 months after transplantation and then annually.

Immunosuppression

Methylprednisolone as an immunosuppressant was initiated in all patients in the immediate postoperative period. When initiating oral intake, this was changed to deflazacort in 86%. From the year 2008 it was changed to prednisone. On the second postoperative day cyclosporine was started at 8 mg/kg/day every 8 h and azathioprine (1 mg/kg/day every 12 h). From 2008, cyclosporine was changed to tacrolimus and from 2010, to sirolimus.

Rejection

With regard to the detection and follow-up of rejection in the initial cases, an endomyocardial biopsy was performed to control rejection. Pathological findings were correlated with the classification of the current ISHLT consensus.16,17 Echocardiographic follow-up was also performed comparing each patient sequentially. In all cases at least three samples were taken at the time of biopsy.

Discharge

In the majority of patients, hospitalization length after transplantation was 20 days during which immunosuppressive levels were taken. Instructions were given to parents regarding taking of the medication. All patients were discharged with an inhibitor of calcineurin, azathioprine and prednisone as well as prophylactic antibiotic with trimethoprim/sulfamethoxazole and oral antifungal. Patients were scheduled to be seen at 15 days, 1 month, 3 months, 6 months and every year for taking immunosuppressive levels.[18]

RESULTS

The indication for transplantation by age group was as follows: for younger infants (1 month to 1 year) was congenital heart disease and for older infants (>1 year-2 years) was due to congenital heart disease (75%). For preschool-age children (>2-6 years) the indication was cardiomyopathy (75%) and in school-age children (>6 years-12 years) it was cardiomyopathy (66%). Finally, for the group of adolescents (>12-18 years) it was cardiomyopathy (50%) (Table 1).

Among the congenital heart diseases observed in our patients were the following: Shone syndrome (one patient), visceral asplenia heterotaxy (two patients), AV and VA discordance (two patients), arrhythmogenic right ventricular dysplasia (one patient), two-way right ventricular outlet with valve dysplasia (two patients), Ebstein anomaly (one patient), hypoplastic left ventricular syndrome (one patient), and pulmonary atresia with intact septum (one patient) (Table 2). Of the patients with congenital heart disease, 41% had a previous surgery. The most common was modified Blalock-Taussig systemic pulmonary shunt.

There were no intraoperative technical complications and all patients came off extracorporeal circulation. Two patients were re-intervened (9%) due to postoperative bleeding. Only two patients died due to primary graft failure (before 15 days after transplant.)

Table 1. Indication for transplant according to age group

Age group	*Cardiomyopathies (%)*	*Congenital cardiopathy (%)*
Young infant 1 month-1 year	–	1
Older infant >1-2 years	1	3
Preschool	2	1
School-age	6	3
Adolescent	3	3
Total	12	11

Table 2. Indication for transplant

Congenital cardiopathy
Shone syndrome
Visceral heterotaxy with pulmonary atresia
Double discordance
Pulmonary atresia with integral septum
Double outlet right ventricle
Ebstein anomaly
Left hypoplastic ventricular syndrome
Cardiomyopathy
Dilated
Familiar

Complications

The incidence of immediate postoperative infections (1 month before the transplant) was 63%, and in some patients was due to the long hospital stay prior to transplant. The most common causes were bacterial infections (78%), viral (7%) and mycotic (7%). The latter were due to a long post-transplant hospital stay but were controlled in a timely manner. Among these infections are nosocomial pneumonia, surgical wound infection, sepsis, peritonitis and mediastinitis. The recipient with a history of a donor positive for CMV was started on gancyclovir. The remaining infected patients were treated with broad-spectrum antibiotics.

The incidence of infections at 6 months from the transplant was 18%, with bacterial infections accounting for 100%. Two patients had an added viral superinfection with CMV and was treated with gancyclovir. One had patient had the addition of tuberculosis and was treated for 18 months with isoniacid, rifampin and ethambutol. This same patient also had resistance to gancyclovir and was treated with gammaglobulin.

The incidence of infection at 1 year was present in 22% of patients. In 60% of patients the etiology was bacterial, which was resolved with antibiotics. In the case of viral infection, 40% presented with CMV infection and were treated with gancyclovir.

The incidence of infections at 3 years after transplant was present in 18% of patients and in 75% the etiology was viral (CMV, parvovirus, EBV). They were treated with gancyclovir and immunoglobulin (parvovirus) as well as the temporary suspension of immunosuppressants.

Rejection

Biopsies were taken in 12 patients (seven patients died 1 month before the transplant) and only baseline echocardiograms were done on the remaining patients due to risk of obtaining the biopsy because of the size of the recipient. In ten patients there was acute grade IA or 0 rejection reported without changes being required in the management of the immunosuppressant. One patient presented grade IIIA rejection, which was managed with methylprednisolone pulses with adequate response. At the 3-year follow-up after transplant, the patient had grade IA rejection or without evidence of rejection. Another patient presented IB rejection that did not respond to adjustment of the doses of the immunosuppressants and progressed after 2 months to grade IIIA. The patient was managed with boluses of methylprednisolone and improved to grade IA; however, due to poor cooperation for management and recurrence to grade IB rejection accompanied by a pericardiac hemorrhage, pericardiocentesis was required on three occasions. One patient who did not have a biopsy done presented severe heart failure. Echocardiogram showed data of dysfunction, which was correlated with what is reported for severe rejection. The patient was managed successfully with muromonab-CD3, anti-CD3 monoclonal antibodies (Orthoclone OKT3, Janssen-Cilag MR).

Mortality

The incidence of immediate postoperative mortality (<1 month) occurred in two patients (8%) who presented primary graft failure. Mortality at 1 month to 3 months from transplant (21%) was due to hospital complications of the patients. The smallest patient presented necrotizing enterocolitis. The remainder of the patients died of septic shock due to nosocomial infection prior to 6 months from the time of transplantation.

Mortality at 3 years from transplantation (8%) was due to rejection due to abandonment of treatment. Mortality at 5 years from the transplant was demonstrated in 17% of patients due to failure of the graft, probably as a result of vasculopathy in one case and due to terminal renal insufficiency in one case.

Mortality according to transplant indication was present as follows: 25% of patients with heart disease had a reported mortality at 4 years as opposed to patients with a history of congenital heart disease where mortality is up to 73% at 5 years of transplant, although the latter presented more immediate postoperative complications (Table 3). Patient survival 1 year after transplantation was 70%; at 3 years 60%; and at 5 years 50% (Figure 1). Survival in

Table 3. Mortality according to etiology and age group

Age group	*Cardiomyopathy*	*Congenital cardiopathy*
Infant 1 month-1 year	–	1
Infant 1-2 years	1	3
Preschool		1
School-age	2	1
Adolescent	2	1
Total	5	7

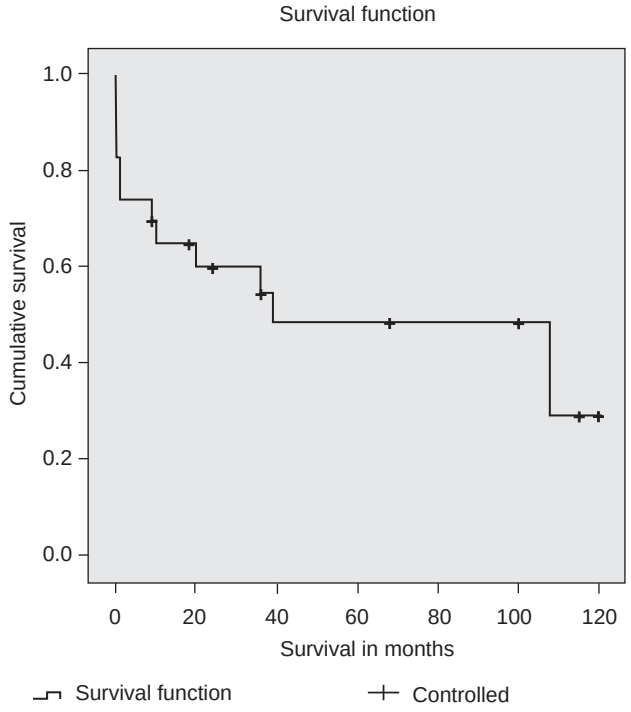

Figure 1. Survival of transplanted patients 2001-2010.

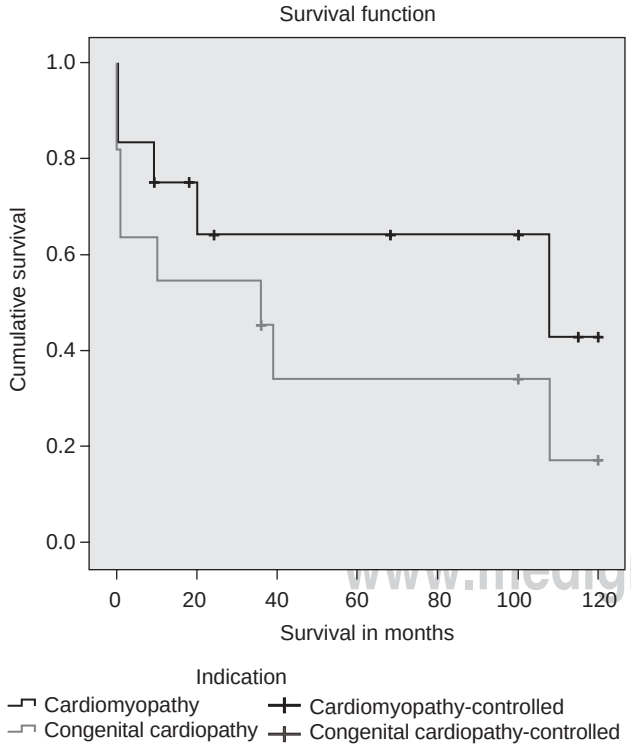

Figure 2. Survival according to transplant indication.

accordance with the indication for transplant was, in first place, for congenital heart disease at 1 year 65%, at 3 years 55% and at 5 years 35%. For heart disease at 1 year it was 80%, at 3 years 75% and at 5 years 65% (Figure 2).

DISCUSSION

The first heart transplants were conducted in adults in the 1960s. However, it was not until the advent of cyclosporine as an immunosuppressant when heart transplantation emerged as a new and successful therapy in terminal cardiac patients and has evolved to date with the emergence of new immunosuppressive agents.

The first pediatric heart transplant took place in 1982.[19] From then until 2010 there have been 532 transplants worldwide. According to reports, 52% of transplants were carried out in North America, 35% in Europe and only 8% in developing countries.[20] In Mexico, the heart transplant program with the highest number of cases is at the HIMFG. This year marks 10 years of pediatric heart transplants in this center.

In this first series of cases the indication for transplantation was slightly higher according to percentage for cardiomyopathy vs. congenital heart disease (one additional patient with cardiomyopathy). This is different from what has been published in the records of the ISHLT that reports a 56% indication for congenital heart disease vs. 40% for cardiomyopathy and includes other indications such as retransplant.[20] This difference is also due to the age of the patient to be transplanted. Worldwide, patients <3 years had congenital heart disease as the predominant indication for transplantation. However, when comparing these results with international reports, it is notable that in North America (U.S. and Canada) there is a greater number of donors for these age groups,[21] whereas in our environment, due to not having as many donors for this age group, multiple palliative surgeries are performed for terminal congenital heart disease without removing these patients from the waiting list. If we compare our series with transplants performed in South America, we can conclude that at the HIMFG a great variety of cardiac pathologies are seen; therefore, an indication of congenital heart disease vs. cardiomyopathy is obtained almost equally, unlike the predominant indication in South America, which is cardiomyopathy.

The survival of patients in the HIMFG was 70% at 1 year, 60% at 3 years and 50% at 5 years after trans-

plantation. There are significant differences with regard to international registrations as the ISHLT reported between 2000 and 2010, survival of 90% 1 year post-transplant, 80% at 3 years and 75% at 5 years, with differences in the registries between Europe and North America.[18,20,22,23] In Europe, 5-year survival rate is up to 80%. These numbers of differences in survival rates are definitely due to the difference in infrastructure. In those centers in the U.S. and Europe there is clear and open information available to the entire population due to the high cultural level and this is different compared with patients who receive treatment at the HIMFG. Despite the exhaustive work done for selection of recipients, there are cases of abandonment of treatment and follow-up of patients, triggering endless complications and death. However, we must also consider the indication for transplantation plays an important role. In patients with congenital heart disease, survival at 1, 3 and 5 years after transplantation is significantly reduced relative to patients who were transplanted for cardiomyopathy. This difference lies mainly in the age of the transplanted patient because this group of patients was <3 years of age, which increases surgical morbidity (some patients had previous surgery) and complications from adverse immunosuppressive reactions. This also occurs internationally. Europe has better survival than North America due to the fact that in North America there are more transplants performed in children with congenital cardiomyopathies.[18,20] We can also say that survival has improved over time. In Mexico, our location is the unique site where pediatric cardiac transplant is performed. Transplants that have been performed from 2007 to date have presented less morbidity than at the beginning of the program. If we take into account that the program is still in its developmental stage, it can be compared with international reports of the first pediatric transplant series (1982-1989) where 1-year survival was 65%, at 3 years 60% and at 5 years 55%.[18] With regard to mortality, infection plays an important role in the first 6 months after transplantation, resulting in the death of 21% of patients due to difficulty in controlling nosocomial infections. This is in contrast to international results where mortality from infection is reported as only 14%.

According to this international registry, there is up to 28% mortality attributed to graft failure due to intraoperative technical failures. At the HIMFG we do not have reports of frequent intraoperative complications. Similar to international reports, from 3 to 5 years after transplantation the greatest challenge has been rejection and graft failure. In our environment, this situation has been very difficult because some patients have been lost to follow-up. For this reason, efforts are ongoing to educate transplant candidates in regard to the comprehensive elements of the program and also the importance of the follow-up of patients who have been transplanted.

Pediatric cardiac transplantation provides effective treatment for a variety of inoperable congenital heart diseases and increases life expectancy in patients with cardiomyopathy. Unfortunately, there is still the need to educate the population about the importance of organ donation and educate parents of heart transplant patients on the essentials for treatment monitoring.

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