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Heart Transplantation in Adult Patients with Congenital Heart Disease

Trasplante cardíaco en adultos con cardiopatías congénitas

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ABSTRACT

Background: Over recent decades, congenital heart disease (CHD) patients have posed new challenges in the management of complications, both of the original condition as of the corrective surgeries that have allowed them to reach adulthood.

Objective: The aim of this study was to report the outcomes and evolution of CHD patients who had been evaluated for transplantation in a tertiary care center.

Methods: Using the institutional database, data from 11 patients with different congenital diseases were evaluated for transplantation. A total of 5 patients underwent transplantation, with a 1.6-year survival rate of 80%. Mortality rate was 66% for patients who were on the waiting list but were not transplanted, and 35% for those who were ruled out due to comorbidities.

Conclusion: Heart transplantation in CHD adult patients present a higher periprocedural risk than in patients with acquired heart diseases. However, those who survive the first post-transplant year have an excellent long-term outcome.

Key words: Adult congenital heart diseases - Heart transplantation - Single ventricle - Transposition of the great arteries - Ebstein's disease - Cirrhosis

RESUMEN

Introducción: En las últimas décadas los pacientes con cardiopatías congénitas (CC) han presentado nuevos desafíos en el manejo de las complicaciones, tanto de la patología originaria como de las cirugías correctoras que les han permitido llegar a la adultez.

Objetivo: Comunicar los resultados y la evolución de los pacientes con CC que hayan sido evaluados para trasplante en un centro de alta complejidad.

Material y métodos: Se utilizó la base de datos institucional, y se analizaron los datos de 11 pacientes evaluados para trasplante con diversas patologías congénitas. Accedieron al trasplante 5 de ellos con una supervivencia a 1,6 años del 80%. Los pacientes que se hallaban en lista y no se trasplantaron tuvieron una mortalidad del 66%, y los descartados por comorbilidades presentaron una mortalidad del 35%.

Conclusión: El trasplante cardíaco en adultos con CC tiene un riesgo periprocedimiento más elevado que para las cardiopatías adquiridas (CA). No obstante, los que sobreviven el primer año postrasplante tienen una excelente evolución a largo plazo.

Palabras clave: Cardiopatías congénitas del adulto - Trasplante cardíaco - Ventrículo único - Trasposición de grandes arterias - Enfermedad de Ebstein - Cirrosis hepática

INTRODUCTION

Over the past decades, there has been an improvement in both technical procedures and clinical care of patients with congenital heart diseases (CHD), resulting in increased survival.

The first phrase of the review article by Martin et al. states: *We are condemned by our own success...*, which fully reflects our present moment regarding CHD.⁽¹⁾

Complications affecting this population are varied. A particularly interesting subgroup includes patients

who, despite undergoing a repair procedure, are in end-stage CHD and are thus considered for transplantation.

Since 1999, the rates of transplantation in CHD patients increased from 2% to 4% of all the transplantations reported to the International Society of Heart and Lung Transplantation (ISHLT) and constitute 11% of the transplantations in patients under 40 years of age. (2, 3)

The decision to include a CHD patient on the waiting list is highly complex. First of all, there are no

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guidelines or conclusive evidence about it. The decision is based on case series, single-center records, and expert opinions (4). Most of the times, the causes for transplantation are not conventional for adult patients with CHD, and the variables determining the progress on the waiting lists are not the ones these patients have.

There is also a certain preconception that transplantation in these conditions is too complex and does not have good results, so it should only be considered in extreme situations -which, on the other hand, are often the situations that contraindicate it. There is a wide spectrum of conditions across CHD that can lead to the need for transplantation, but there is no well-defined time to do it in each of them.(5)

METHODS

A retrospective analysis of the institutional database was carried out, and data were collected from adult patients (>18 years) who were evaluated for heart transplantation due to CHD.

Quantitative variables were described as mean and standard deviation, or median and interquartile range, as appropriate. No statistical analyses of differences were performed due to the scarce number of patients.

Ethical considerations

The protocol design of the ARGEN-IAM-ST registry was evaluated and approved by the Bioethics Committee of the Argentine Society of Cardiology, and was subjected to evaluation of the participating centers' committees, depending on local regulations and institutional policies.

RESULTS

Since the Adults with CHD Program was launched in February 2015 at *Hospital Italiano de Buenos Aires*, 207 patients have been followed up. Among these patients, 22% suffer from complex heart diseases, with recommended follow-up in tertiary care centers by professionals specialized in CHD. (5) Median age is 33 years (CI25-75: 25-43) for all the patients, and 28 years (CI25-75: 24-35) for patients with complex heart diseases.

A total of 11 patients have required evaluation for transplantation. The conditions for those requirements have been complications of total right ventricular bypass in its various forms in 5 patients; transposition of the great arteries (d-TGA) with Senning surgery and systemic ventricular dysfunction in 2 patients; and congenitally corrected transposition of the great arteries (l-TGA) in 2 other patients; a female patient with dextrocardia, *situs inversus* (SI), single right ventricle and single atrioventricular (AV) valve with severe pulmonary stenosis, undergoing Glenn's surgery in childhood, in whom the bypass was never completed, and finally, a patient with Ebstein's disease. (Table 1)

The causes for which patients with Fontan-Kreutzer type circulation were evaluated for transplantation were systemic ventricular failure (1 pa-

tient), protein-losing enteropathy (1 patient), and cirrhosis (3 patients). Among these cases, one was not eligible for transplantation because the professional team considered that the patient's clinical/surgical risk was unacceptable. Both patients with d-TGA and oximetry correction were evaluated due to systemic ventricular failure and functional class deterioration.

The two patients with l-TGA underwent transplantation; one due to homograft dysfunction as a result of pulmonary atresia worsened by endocarditis, and the other due to systemic ventricular failure, relapsing arrhythmia and hemodynamic decompensation. The patient with SI and single ventricle with pulmonary stenosis, who underwent Glenn surgery only, was evaluated due to impaired functional capacity, cyanosis and recurrent arrhythmias, but was ruled out for unacceptable risk.

Finally, the patient with Ebstein's disease underwent transplantation due to right ventricular dysfunction and arrhythmias refractory to medical and electrophysiological treatment. (Table 1)

Of the three cases who were ruled out for transplantation, the patient with right ventricular bypass died two years later due to liver disease. The patient with SI and single ventricle suffered a transient ischemic attack (TIA) and is currently in functional class III-IV, and the third patient improved his functional class but has not been included in the waiting list yet.

Of the three patients on the waiting list who were not transplanted, two patients with l-TGA died while on the list, one due to hemorrhagic stroke likely associated to his endocarditis, and the other as a result of arrhythmia and systemic ventricular failure, requiring a ventricular assist device. Waitlist time was 10 days for the first case, and 3 days for the second patient, who was referred to emergency after device implantation. The patient with protein-losing enteropathy is still on the elective list.

Finally, 5 patients underwent transplantation. The median number of days on the waiting list was 41 (CI25 - 75, 34-94) for those on the urgency list; 27 (1 patient) for the emergency list, and no patient on the elective list has been transplanted yet.

Mean pump time was 245 minutes (CI95, 157-333), and mean clamping time was 247 minutes (CI95, 198-296). Circulatory arrest was needed in two of the three patients with single-ventricle physiology. A patient with Fontan-Kreutzer circulation and cirrhosis, who progressed with severe intraoperative bleeding, graft failure and circulatory assistance requirement after a technically complex transplantation, died during hospitalization. The patient had a postoperative stroke and progressed to brain death on the 6th day after surgery.

The patient with Ebstein's disease presented with a distal embolism in the left lower limb, progressing to severe ischemia and requiring infrapatellar amputation.

Table 1. Congenital heart disease, age at evaluation, prior surgeries, time since corrective surgery, and reason for transplantation.

Condition	Age (years)	Prior surgeries	Time since corrective surgery (years)	Reason for pre-transplant evaluation	Outcome
Transplanted patients (n = 5)					
Tricuspid atresia + TGA + VSD + pulmonary stenosis (IIB)	32	- Subclavian-pulmonary artery anastomosis - Atriopulmonary anastomosis	26	Systemic ventricular failure	Very good
D – TGA	31	Senning surgery	30	Functional class deterioration	Very good
Pulmonary atresia with intact septum	19	- Subclavian-pulmonary artery anastomosis - Glenn surgery - Total extracardiac conduit bypass	14	Cirrhosis	Very good
Single right ventricle (with common AV valve) + pulmonary stenosis	21	- Glenn surgery - Total extracardiac conduit bypass	14	Cirrhosis	Died
Ebstein's disease	25	- No surgery	---	Refractory arrhythmia and hemodynamic decompensation	Amputation
Patients ruled out for transplantation (n = 3)					
Dextrocardia + <i>situs inversus</i> + single right ventricle with single AV valve + pulmonary stenosis	42	- Right subclavian-pulmonary artery anastomosis - Left subclavian-pulmonary artery anastomosis - Glenn surgery	30	Functional class deterioration and cyanosis	TIA
Tricuspid atresia + VSD + pulmonary stenosis (IB)	40	- Subclavian-pulmonary artery anastomosis - Atriopulmonary anastomosis Atriopulmonary conversion to extracardiac conduit	34 (From the pulmonary atrium)	Cirrhosis	Died
D – TGA	40	- Senning surgery	39	Functional class deterioration	Functional class improvement
Non-transplanted patients on the waiting list (n = 3)					
L – TGA + VSD + pulmonary atresia	40	- Right subclavian-pulmonary artery anastomosis - Left subclavian-pulmonary artery anastomosis - Atriopulmonary anastomosis - Atriopulmonary conversion to extracardiac conduit	33 (From the pulmonary atrium)	Protein-losing enteropathy	Still on the waiting list
L – TGA + pulmonary atresia + VSD	20	- Subclavian-pulmonary artery anastomosis - Conduit + LV-PA homograft	15	Systemic ventricular failure and LV-PA homograft stenosis	Died
L – TGA + VSD	32	No surgery	---	Refractory arrhythmia and hemodynamic decompensation	Died

D – TGA: Transposition of the great arteries; L-TGA: Congenitally corrected transposition of the great arteries; VSD: Ventricular septal defect. AV: Atrioventricular

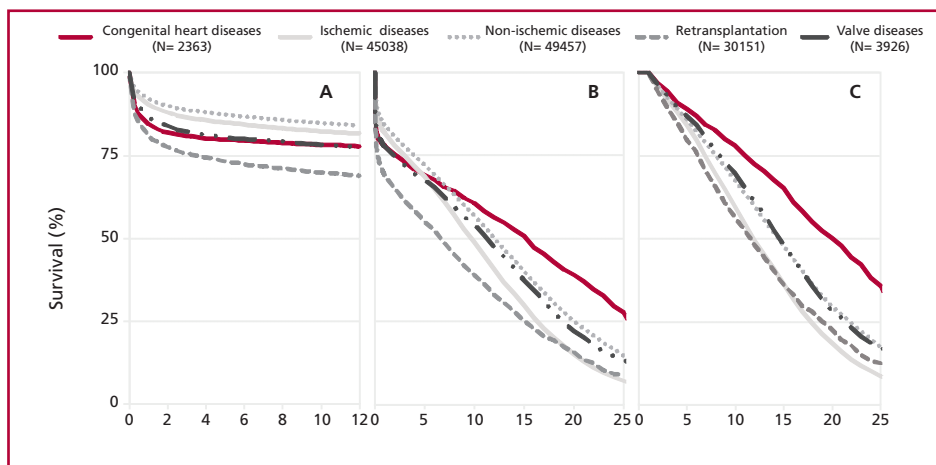


Fig. 1. Twelve-month (A) and long-term total mortality (B) and mortality with survival within the first post-transplant year (C) depending on etiology. (Adapted from: ISHLT - International Society of Heart and Lung Transplantation - 2018; available at: <http://www.isHLT.org/>).

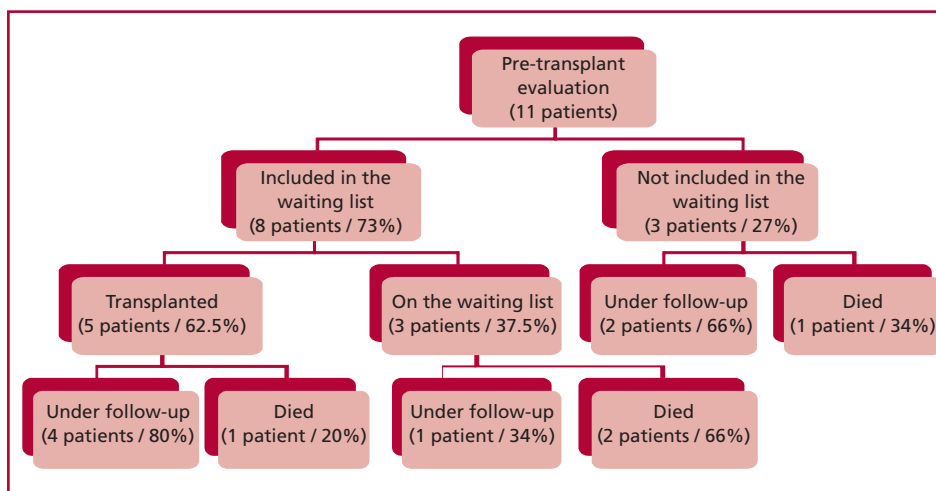


Fig. 2. Transplantation Program for Adults with Congenital Heart Diseases (Institute of Cardiovascular Medicine - Hospital Italiano de Buenos Aires 2015-2018).

The average follow-up period of transplanted patients was 590 days (1.6 years), and to date, their survival rate is 80%. Discharged patients have required no rehospitalization for any complication, and no patient has been lost to follow-up.

DISCUSSION

Due to their distinctive characteristics, patients with CHD are a complex population as far as transplantation is concerned. Those characteristics put them at a very high peri-transplant risk. Although in the short term (30 days after transplantation) mortality is higher than in patients transplanted for other etiologies (16% for CHD vs. 10% for ischemic diseases, for example), in the long term this ratio is reversed, and is similar at 5 to 8 years after transplantation. In fact, the mean post-transplant survival rate is 20 years for CHD patients who survived the first year, significantly better than for other etiologies. (3, 6)

Recent guidelines for the management of CHD recommend that cardiologists should consider early referral to a transplant center when transplantation becomes a relevant clinical consideration. It is also ad-

visable to consider the possibility of transplantation or ventricular assist device as a backup, before other high-risk palliative or corrective surgery is pursued. (5)

In these diseases, there is no variable to predict the right time to undergo transplantation or the risk it will entail. Worsening of the cardiopulmonary exercise test, recurrent hospitalizations, symptoms of heart failure, protein-losing enteropathy, or cirrhosis could be variables that indicate the need but not the right time for transplantation. (6)

To the question: Do all congenital heart diseases have the same risk for transplantation? The answer is no; several records document that patients undergoing transplantation with biventricular physiology have significantly lower mortality rate at both 30 days and one year after transplantation compared with those with univentricular physiology. (7, 8)

In a study on death predictors in failing Fontan patients requiring transplantation, Griffiths et al. found out that those patients undergoing transplantation with ventricular dysfunction had lower mortality rate than those with liver disease or protein-losing enter-

opathy. In turn, among those who were not indicated for transplantation because of their comorbidities, patients with ventricular dysfunction had lower mortality rate than those who underwent transplantation for other reasons. (9)

Due to the anatomical alterations and surgical history these patients present, the surgeon has to face a hostile thorax at the moment of surgery, thus increasing the surgical times and the chances of complications.

Although this has not been the case in our sample, the waiting time for heart transplantation in CHD patients is usually longer than for patients with acquired heart diseases. This is basically because the criteria for urgency or emergency have been developed taking into account the problems or complications of patients with acquired heart diseases, mostly associated with left ventricular failure and their therapeutic needs.

Patients with CHD generally spend more time on the waiting list, at a lower urgency status, their chances to undergo transplantation are significantly lower, and their waitlist mortality rate is higher than that for patients with other etiologies. (10, 11). In an analysis carried out on the UNOS (United Network for Organ Sharing) registry between 2005 and 2009, Everitt et al. found out that patients >18 years with acquired heart diseases have 50% more chances of being transplanted at any given time than CHD patients.

In turn, access to ventricular assist devices and defibrillators is underexploited in this population. This results in a large percentage of sudden deaths and other parenchymal failures due to poor tissue perfusion, with worse general and nutritional conditions that overshadow the peri-transplant prognosis. (12)

Due to the large number of surgeries in the course of their lives, these patients have a high chance of being sensitized. The literature states that sensitization >10% has a worse prognosis, and when it is >25% it presents a greater mortality rate. Although sensitization was not present in all of our patients, those who were sensitized had an average of 49%. At the same time, management of immunosuppression is less strict in CHD patients than in other etiologies, with lower induction rate and use of corticoids. (4)

CONCLUSIONS

We conclude that it is necessary to restrict the indication for reoperation, consider transplantation before extreme patient deterioration, manage immunosuppression appropriately, and, above all, adapt the waiting lists so that the risk conditions of CHD patients are taken into account. Therefore, immediate survival

after transplantation could be significantly improved. If we manage to improve the outcomes at 30 days post-transplant, we will increase the life expectancy and quality of life of our patients.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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