Orthotopic Heart Transplantation: Results from the Hospital Universitario Fundación Favaloro

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SUMMARY

Background
The favorable outcomes achieved during four decades of clinical experience have consolidated heart transplantation as the treatment of choice of refractory heart failure.

Objective
To report the outcomes of patients undergoing orthotopic heart transplantation at the Hospital Universitario Fundación Favaloro during 16 years of follow-up.

Material and Methods
A total of 335 consecutive orthotopic heart transplantations performed in 333 patients from February 1993 to December 2009 were retrospectively analyzed. Follow-up was 94%. Seven percent corresponded to pediatric heart transplantation and 2% to heart-kidney transplantation. Thirty five percent of patients had ischemic cardiomyopathy. Transplants were elective procedures in 42% of cases (142 patients) and 58% (193 patients) were urgent/emergency procedures. Survival was analyzed using Kaplan-Meier curves.

Results
Survival rates at 1, 5, 10 and 15 years were 80%, 74%, 71% and 65%, respectively. There were no significant differences between elective and urgent/emergency procedures. Survival was also similar for the different etiologies, even in patients with Chagas cardiomyopathy. In-hospital mortality was 12.5%, with no significant differences between elective and urgent/emergency procedures. After the first year, the incidence of severe cellular rejection was < 3%. The global incidence of humoral rejection was 4.5%. Lymphoproliferative syndrome was diagnosed in 11 patients (3.5%). Twenty one percent of patients developed kidney failure, 24% diabetes mellitus, 69% hypertension and 70% dyslipemia.

Conclusion
In our center, survival rates after heart transplantation at 1, 5, 10 and 15 years were 80%, 74%, 71% and 65%, respectively.

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Key words > Heart Transplantation - Cardiomyopathy - Heart Failure - Circulatory Assistance

Abbreviations >

DNA	Desoxirribonucleic acid	**PCR**	Polymerase chain reaction
GVD	Graft vessel disease	**HTx**	Heart transplant
HLA	Human leukocyte antigen	**INCUCAI**	Instituto Nacional Central Único Coordinador de Ablación e Implante (Central Unique National Institute Coordinator of Ablation and Implant)
ISHLT	International Society of Heart and Lung Transplantation		

BACKGROUND
The favorable outcomes achieved during four decades of clinical experience have consolidated heart transplant (HTx) as the treatment of choice in selected patients with heart failure refractory to any other treatment. Today, HTx is the therapeutic option that changes with great impact the course of the natural progress of advanced heart failure. The

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objective of this study has been to update the report of the outcomes of patients undergoing orthotopic HTx (1) performed at Hospital Universitario Fundación Favaloro during a follow-up of 16 years.

MATERIAL AND METHODS

A total of 335 HTx consecutive orthotopic transplants in 333 patients between February 1993 and December 2009 were retrospectively analyzed. For statistically purposes, we reviewed data from medical records, maintaining patients' confidentiality. Follow-up was 94% and the median follow-up was 7.7 years.

Orthotopic HTx was performed in 98% of the patients, and heart-kidney transplant, in 2%. A 7% corresponded to pediatric HTx. In 42% (= 143), transplants were emergency procedures (requiring mechanical circulatory or respiratory support); in 16% (n = 50), they were urgent (requiring inotropes), and the remaining 42% were performed as elective procedures. Aortic counterpulsation balloon pump was necessary in the emergency subgroup, 85% (n = 118); 4% required only mechanical respiratory support, 11% (n = 15) were under complex mechanical circulatory support, and one patient needed extracorporeal membrane oxygenation.

Two patients were repeated heart transplant; one of them due to primary graft failure without multi-organ failure, requiring mechanical ciruculatory support with Levitronic; repeated heart-kidney transplant was elective in the other patient due to graft vessel disease (GVD) and cardiorenal failure. For late survival analysis, patientes who repeated heart transplant were considered as two new patients.

Recipients mean age was 47 ± 16 years (0-74), and 80% of them were men. Cardiomyopathies were the following: ischemic-necrosis (35%), idiopathic cardiomyopathy (35%), valvular disease (7%), chagasic cardiomyopathy (6%), restrictive atrial septal defect (2.5%), congenital defects (2.5%), ventricular hypertrophy (5%), familiar cardiomyopathies (2.5%), myocarditis (1.5%), peripartum and alcoholic cardiomyopathies in 3 patients, non-compacted myocardium and adriamycin toxicity in 2 patients, cardiomyopathy associated with myopathy and due to Borjeson syndrome in 1 patient, respectively.

Most implanted hearts came from donors who died of traumatic brain injury, with a mean age of 26 years. The surgical technique used was the atrio-atrial anastomosis, described by Lower and Shamway; over the past years, the bicaval anastomosis technique was introduced. (2)

Immunosuppressive induction therapy with monoclonal or polyclonal antibodies was only used in a selected subgroup of high-risk patients (cross-match vs panel > 10%, pretransplant mechanical circulatory support, pediatric patients with kidney failure or heart-kidney transplant, and repeated transplant). (3) The maintenance immunosuppressive regimen at the early stage was based on a triple regimen that combined calcineurin inhibitors (cyclosporine), an antiproliferative agent (azathioprine), and glucocorticoids. In recent years, the agents used have been replaced; tacrolimus and sodic or mofetil mycrophenolate were the most common therapeutic options, which reduced the use of corticosteroids during the first year. More recently, mTor inhibitors (rapamycin or everolimus) have been incorporated in patients with kidney failure or graft vessel disease (GVD). (4)

The follow-up to detect acute rejection was performed through endomyocardial biopsies according to the protocol of institutional surveillance, using the International Society for Heart and Lung Transplantation (ISHLT) grading system. (5) At the early stage (1-2 weeks), intravenous pulses of corticosteroids were administered for moderate-rejection treatment, and baseline immunosuppressive regimen was adjusted for late-rejections. In rejections ≥ 3A grade with no hemodynamic involvement, methylprednisolone pulses were used for three days, and in severe rejections associated with hemodynamic involvement, thymoglobulin therapy was indicated. Other indications for endomyocardial biopsy included clinically suspected rejection or myocarditis, neglect and/or changes in immunosuppresor regimen, cessation of corticosteroids, drug interactions, and control after anti-rejection therapy.

Diagnostic criteria for humoral rejection were clinical evidence of grraft dysfunction with reduced left ventricular function, histological changes with capillary endothelium lesion, macrophages in capillaries, cell infiltration (neutrophils), interstitial edema, hemorrhage, immunofluorescent deposits of the immunoglobulins G or M, detection of antibodies against human leukocyte antigens (anti HLA) class I or II, or HLA antibodies in serum. (6)

Coronary angiography and coronary endovascular ultrasound were performed to detect GVD within the first year after transplant. (7) Since their discharge, all patients were administered aspirin and statins. (8) A strict metabolic control was performed for detection and early treatment of high blood pressure, dyslipidemia, diabetes, and osteoporosis.

To select patients who underwent heart-kidney transplant, two creatinine clearances < 40 ml/h were required, performed with cimetidine and fresh analysis of fresh urine sediment.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviaton, and categorical variables as frequencies in percentages. To compare qualitative variables, the test of chi square was used. Event-free survival was measured using Kaplan Meier curves. Actuarial survival differences between two groups were measured using the log-rank test. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

In our center, a total of consecutive, de novo transplants in 333 patients were performed; two of them underwent repeated transplant due to GVD and primary graft failure. The number of transplants has increased in recent years.

Survival

Comparative hospital mortality was 12.5% versus 16%; no significant differences were observed between the elective versus the urgent/emergency transplant procedures (p = 0.06). The main cause of hospital mortality was the primary graft failure (35%) with severe ventricular dysfunction but no evidence of immunological or anatomic cause to justify it.

Chance of actuarial survival at 1, 5, 10, and 15 years was 80%, 74%, 71%, and 65%, respectively (Figure 1). Excluding the first year after transplant (conditional survival), survival at 5, 10, and 15 years was 92%, 89%, and 74%.

During follow-up, the most common causes of mortality were sepsis (30%) and multi-organ failure (17%) (Figure 2).

Urgent/emergency transplants increased in recent years (Figure 3). The condition of elective versus urgent/emergency procedure showed no significant differences in global mortality (log-rank test p = 0-8). Figure 4 shows the different types of advanced mechanical circulatory support used as a bridge to transplant. Survival analysis by etiology of cardiomyopathy did not show significant differences either (p = 0.1).

The comparative analysis of heart-kidney transplant survival showed that it was similar to that of patients with HTx without kidney failure (log-rank test p = 0.4) and significantly higher than in those undergoing HTx with creatinine clearance < 40 ml/h (log-rank test p = 0.05). Still, HTx patients without kidney failure had a significantly higher survival versus those with creatinine clearance < 40 ml/h (log-rank test p = 0.01) (Figure 5).

Recipients with Chagas disease

Patients with chagasic cardiomyopathy showed a similar survival to that showed by recipients without Chagas disease (p = 0.7). Disease reactivation rate was 40%, with a favorable clinical evolution under benznidazol therapy. Clinical presentation varied, with involvement of different organs; at skin level, the presence of painful subcutaneous nodes was typical; the involvement of the heart graft was manifested as myocarditis, but the central nervous system was not involved.

Cellular, humoral rejection, and graft vessel disease

During follow-up, excluding the first year after transplant, severe acute cellular rejection was lower than 3%.

Humoral rejection was present in 4.2% (n = 14)

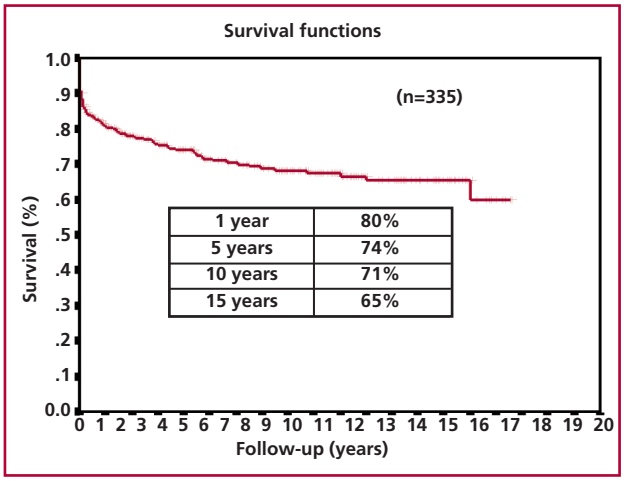

Fig. 1. Kaplan-Meier survival curve.

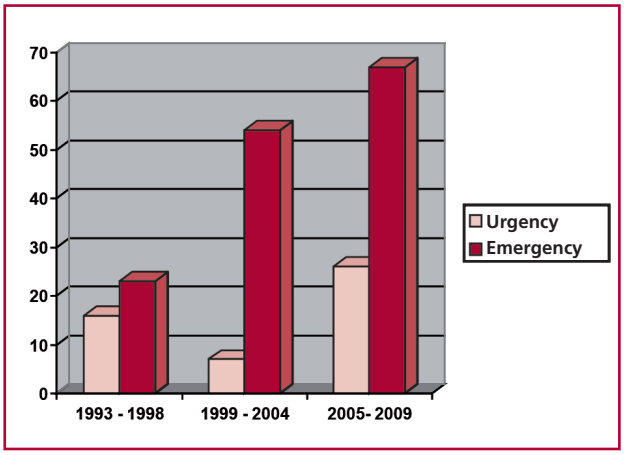

Fig. 3. Urgent/Emergency heart transplant by periods.

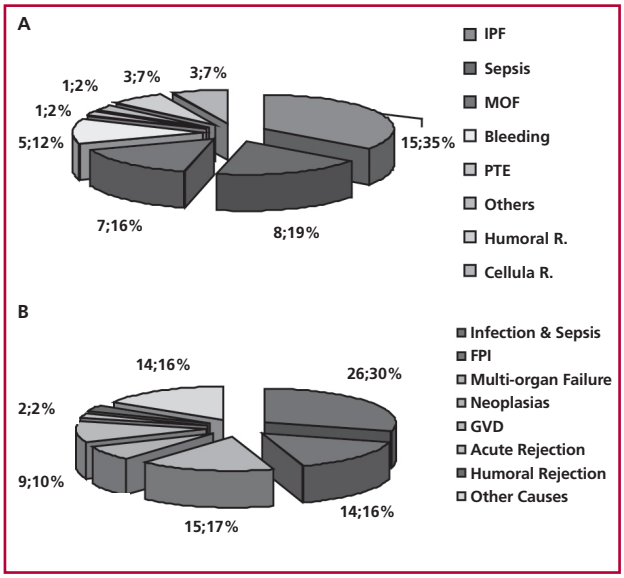

Fig. 2. A. Hospital mortality causes. **B.** Late mortality causes.

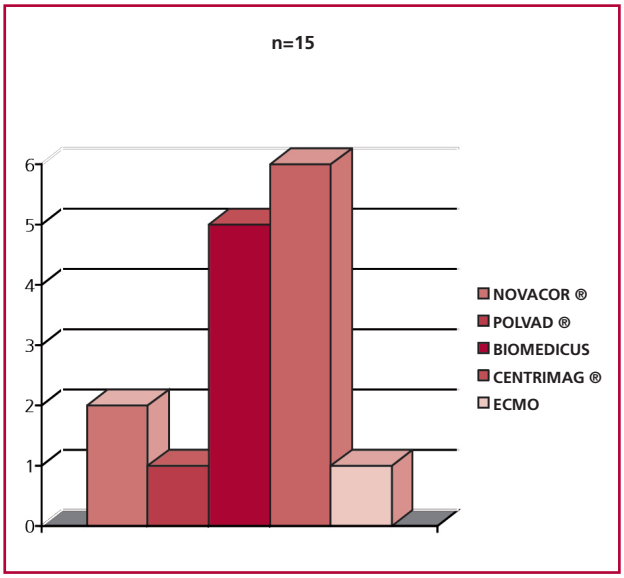

Fig. 4. Emergency heart transplant. Advanced mechanical circulatory support.

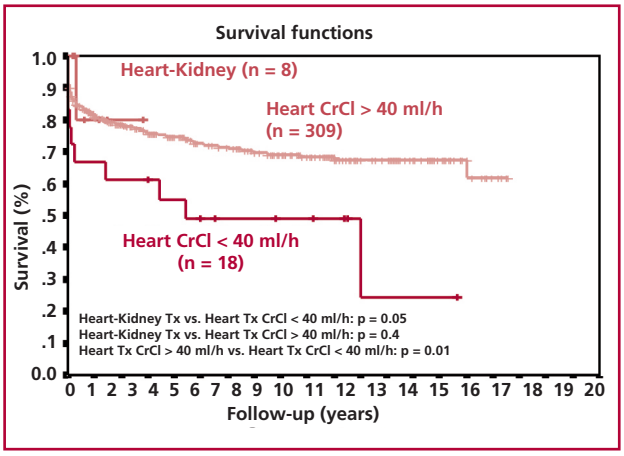

Fig. 5. Comparative survival curve. Tx: Trasplant. CrCl: Creatinine clearance.

of the patients. Clinical risk factors of immunological sensitization included previous surgery in 5 patients (35%), transfusions in 6 patients (50%), pretransplant mechanical circulatory support in 4 patients (28%), and multiparity in women. Only 3 patients presented with positive direct cross-match vs panel > 10%. Humoral rejection with a negative direct cross-match was diagnosed in 11 patients. In 92% of the patients, humoral rejection developed early (30 days after transplant), and 50% presented with hemodynamic involvement. The treatment of choice was a combination of plasmapheresis and thymoglobulin, followed by cyclophosphamide or hyperimmune immunoglobulins. Hospital mortality in this group was 27% and survival at 1.5 and 10 years was 78.5%, 50% and 50%, respectively.

GVD detection was performed by endoluminal coronary ultrasound, which showed a prevalence of 63%; significant angiographic lesions were found in 19% of the patients.

Morbidity

Morbidity during follow-up included dyslipidemia in 70% of the patients, high blood pressure in 69%, de novo diabetes mellitus in 24%, and kidney failure (creatinine > 1.5 mg/dl) in 21% of the patients. Only 1% of the patients had kidney failure requiring hemodialysis. Post-transplant lymphoproliferative syndrome was diagnosed in 11 patients (3.5%); in general, its onset was late, at more than 12 months of HTx, with extranodal involvement. The treatment of choice was a sharp reduction in immunosuppressive levels, rituximab therapy in patients with positive CD 20 flagging, and 50% of the patients received chemotherapy. Mortality was 50% and its cause was the progression of the disease or sepsis. They presented no significant rejection episodes.

Pediatric recipients

Among the pediatric patients, 60% was in the age group of 0.6-18 years, and emergency and urgency transplants were performed in 60% and 17%, respectively. Survival at 1, 5, and 10 years was 72%, 63%, and 63%, respectively, without significant differences with the overall population (p = 0.3).

Heart-kidney recipients

Heart-kidney transplant recipients (n = 8) had nephropathy secondary to nephroangiosclerosis (with creatinine clearance < 40 ml/h) associated with their cardiomyopathy. Neither renal biopsy nor HLA matching were performed prior to transplant. Mean age was 50 years, and all patients were men. Their mean creatinine was 3.7 mg/dl and 43% of them were under hemodialysis. Urgent/emergency transplant was performed in 6 patients. None of them developed severe cellular rejection of heart graft and only 2 patients had renal graft dysfunction, who were performed renal biopsy after transplant, without rejection. There was no hospital mortality, and only one patient died at one year of follow-up due to sepsis. Figure 5 shows comparative survival of patients with HTx with and without kidney failure.

DISCUSSION

In 1968, in Argentina, Dr. Miguel Bellizi performed the first heart transplant in the Clinica Modelo de Lanús; it was transplant number nineteen worldwide. The patient survived 94 hours after surgery. In the 1980s, Dr. René G. Favaloro organized the first national heart transplant program in Argentina, in the healthcare center Sanatorio Güemes, where the first HTx was performed, with long-term survival. In 1989, the first text on heart transplant was published in Latin America. (9)

The Central Unique National Institute Coordinator of Ablation and Implant (INCUCAI) has reported more than 945 heart transplants in Argentina between 1995 and 2009, (10) which represents an average of 70-80 surgeries per year in the last decade. At present, eight provinces in the country have a heart transplant program, and there are 23 licensed health care facilities to perform this surgery, with a low relationship in the number of transplants per center.

The clinical profile of recipients has not changed over these years; mostly, they are men with a mean age of 47 years who have ischemic-necrotic dilated cardiomyopathy in functional class III-IV. However, the scarcity of optimal donors in recent years has led to increased time and mortality on the waiting list; this resulted in resorting to older donors, with no impact on mortality according to different reports, (11) including the outcomes of our group. (12) In our center, survival at 1, 5, 10, and 15 years was comparable to that from the registries published by the ISHLT. In recent years, reported survival in patients with HTx shows better outcomes due to optimized immunosuppressive therapy and management of infections. (13) Also, there has been an increased number of patients with

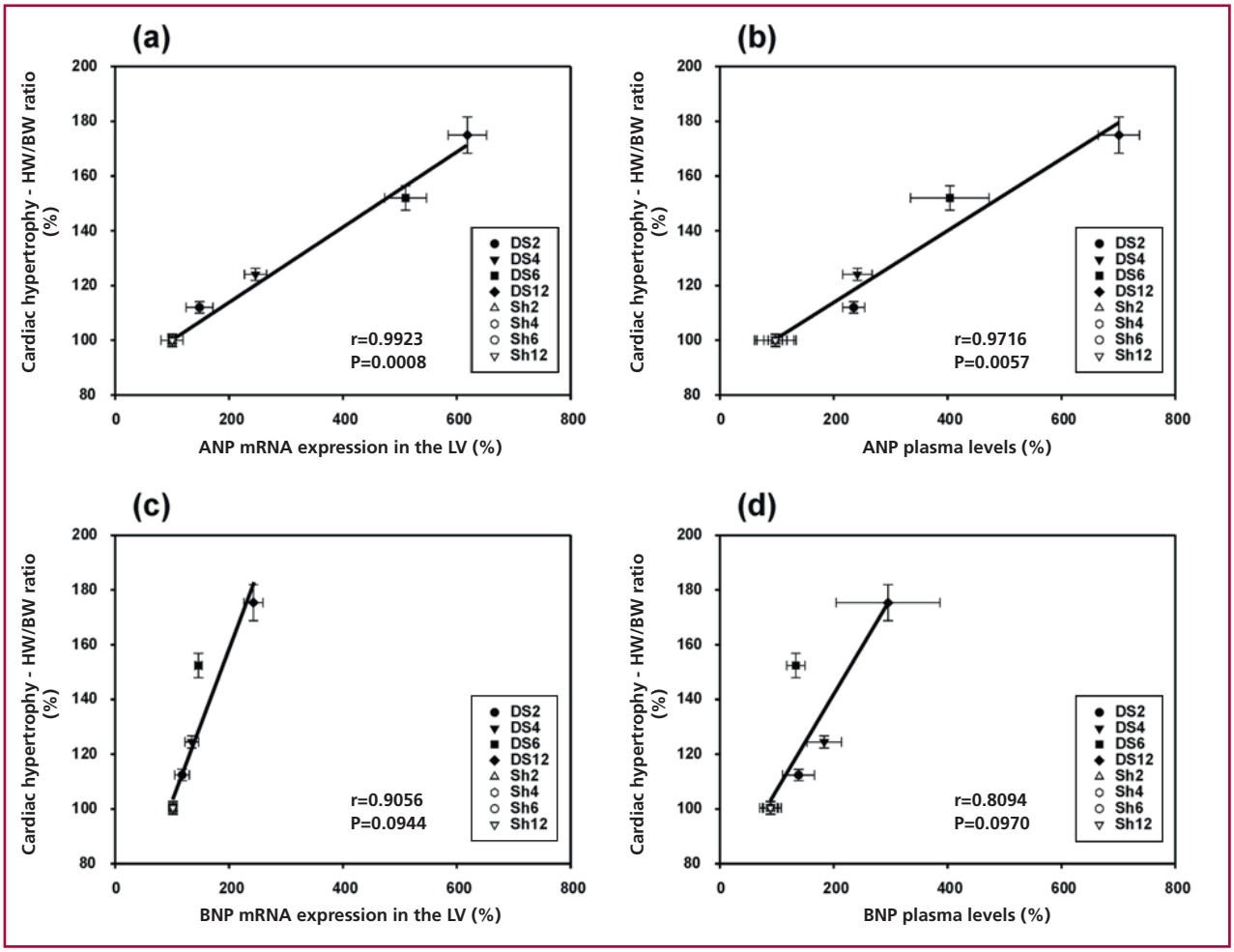

Fig. 4. Correlation between cardiac hypertrophy and ANP expression in the LV (panel a), plasma ANP levels (panel b), BNP expression in the LV (panel c) and BNP plasma levels (panel d). Each dot in the diagram represents mean ± SEM for each group.

urgent/emergency transplant in recent years. Despite the higher risk for this population, this tendency has not susbstantially changed neither hospital nor global mortality. We believe that the vital support with drugs and ventricular assist device in due time to prevent or improve multi-organ failure are responsible for this evolution. When selecting high-risk patients, those with active uncontrolled infection or simultaneous failure in three or more organs were excluded. Regarding mortality analysis based on the main etiologies of cardiomyopathy, no statistically significant differences were detected. Survival in patients with chagasic cardiomyopathy was similar to that of non-chagasic patients. Chagas disease is an endemic infectious condition in Latin America. The etiological agent is the Trypanosoma cruzi, and its form of transmission is vectorial (Triatoma infestans), placental, through breastfeeding or blood transfusions. (14) Its prevalence is 16-18 millions, out of which 2.64 millions correspond to Argentina. Epidemiological studies estimate that 25-30% of the infected patients will develop a chronic chagasic cardiomyopathy, and 18% will progress to end-stage heart failure, associated with high mortality. (15) Indicating HTx in this subgroup of patients was controversial because of the risk of relapse of the disease. In 2001, Bocchi and Fiorelli published the Brazilian experience of HTx in 117 chagasic patients, with a slightly better survival than that of the non-chagasic HTx population. (16) This turns the HTx into an effective therapeutic alternative at the end-stage of the infectious disease with high prevalence in Latin America.

Reactivation monitoring of Chagas disease was conducted in a systematic way, with parasitological tests to determine the parasite in blood (strout) and with DNA amplification techniques for parasite through a polymerase chain reaction (PCR) in blood and tissue with higher diagnostic sensitivity. This allowed to implement an early treatment with benznidazol, 5 mg/kg/day for 60 days, with total remission in all cases. (17)

In 2006, the heart-kidney transplant program was implemented in our center. The incidence and prevalence of severe kidney failure in advanced heart failure are high and go on increasing. Kidney failure is a known predictor of pre-HTx bad prognosis

associated with high morbidity and mortality during follow-up. In our series, 21% of the patients developed kidney failure despite having optimized the use of calcineurin and m-TOR inhibitors. Only 1% required chronic hemodialysis, and two patients received renal transplant at late follow-up. Heart-kidney transplant combined with single donor may be a therapeutic option in selected patients with severe cardiomyopathies and irreversible kidney failure. Since then, heart-kidney transplant was performed in 8 patients, and their survival was significantly higher than that for patients with HTx and creatinine clearance < 40 ml/h, which shows the positive impact of the kidney transplant in this subgroup of patients. (18, 19) Similar outcomes were reported by the international registry, which show a higher mortality rate in patients who needed kidney transplant due to chronic kidney failure after HTx. (20)

CONCLUSIONS

Heart transplant in selected patients with advanced refractory heart failure (stage D) is the therapeutic option that offers a survival rate which is higher than that of conventional treatment, even in patients with circulatory assistance.

Survival analysis in our center is comparable with data reported by other international registries. (21, 22)

RESUMEN

Trasplante cardíaco ortotópico: resultados del Hospital Universitario Fundación Favaloro

Introducción
Los resultados favorables a lo largo de cuatro décadas de experiencia clínica han consolidado al trasplante cardíaco como el tratamiento de elección en la insuficiencia cardíaca refractaria a todo tratamiento y lo convierten en la terapéutica de elección.

Objetivo
Comunicar los resultados de pacientes con trasplante cardíaco ortotópico realizados en el Hospital Universitario Fundación Favaloro con 16 años de seguimiento.

Material y métodos
Se analizaron retrospectivamente 335 trasplantes cardíacos ortotópicos consecutivos efectuados en 333 pacientes entre febrero de 1993 y diciembre de 2009. El seguimiento fue del 94%. El 7% fueron trasplantes cardíacos pediátricos y el 2%, cardiorrenales. El 35% de los pacientes eran portadores de miocardiopatía isquémico-necrótica. En el 42% (142 pacientes) fueron electivos y en el 58% (193 pacientes) se realizaron en urgencia/emergencia. La supervivencia se analizó mediante curvas de Kaplan-Meier.

Resultados
La supervivencia global a 1, 5, 10 y 15 años fue del 80%, 74%, 71% y 65%, respectivamente. La condición de electivo versus urgencia/emergencia no mostró diferencias significativas en la mortalidad global. Tampoco la etiología de la miocardiopatía, incluso en pacientes con miocardiopatía chagásica. La mortalidad hospitalaria fue del 12,5%, sin diferencia significativa en los trasplantes electivos versus urgencia/emergencia. Luego del primer año, la incidencia de rechazo celular grave fue < 3%. La incidencia global de rechazo humoral fue del 4,5%. Se diagnosticaron síndromes linfoproliferativos en 11 pacientes (3,5%). Desarrollaron insuficiencia renal el 21% de los pacientes, diabetes mellitus el 24%, hipertensión arterial el 69% y dislipidemia el 70%.

Conclusión
En nuestro centro, la supervivencia postrasplante cardíaco a 1, 5, 10 y 15 años fue del 80%, 74%, 71% y 65%, respectivamente, comparable a la de los registros internacionales.

Palabras clave > Trasplante cardíaco.- Miocardiopatías - Insuficiencia cardíaca - Asistencia circulatoria

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