

Combined heart-kidney transplantation in Mexico

Guillermo Careaga-Reyna^{1*}, Hugo Jesús Zetina-Tun², Carlos Alberto Lezama-Urtecho³,
José Mariano Hernández-Domínguez⁴ and Marlene Santos-Caballero⁵

¹Directorate General; ²Thoracic Organ Transplantation Clinic; ³Cardiothoracic Surgery Division; ⁴División of Transplantation and Diagnostic Auxiliaries; ⁵Department of Transplantation, High Specialty Medical Unit, Hospital General Dr. Gaudencio González Garza, Centro Médico Nacional La Raza, Mexico City, Mexico

Abstract

Background: In our country, heart and kidney transplantation is a novel option for treatment of combined terminal heart and kidney failure. This program began in 2012 for selected patients with documented terminal heart failure and structural kidney damage with renal failure. **Description of cases:** Between January 1, 2012 and April 30, 2016, we made 92 orthotopic heart transplantations. In five of these cases the heart transplantation was combined with kidney transplantation. **Results:** There were three male and two female patients with a mean age 25.6 ± 5.2 years (range, 17-29). The patients improved their renal function and the heart transplantation was successful with an improved quality of life. One patient died from abdominal sepsis. The other patients are doing well. **Conclusion:** The combined heart-kidney transplantation is a safe and efficient procedure for patients with structural kidney and heart damage as a cause of terminal failure. (Gac Med Mex. 2016;152:699-703) **Corresponding author:** Guillermo Careaga-Reyna, gcareaga3@gmail.com

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Introduction

Although infrequently performed, combined heart and kidney transplantation is accepted as a therapeutic option for patients with heart end-stage failure and irreversible renal damage¹. This treatment option is not new; the first report of heart and kidney combined transplantation is from 1978², and it has slowly increased in the world³, with encouraging results, with both organs obtained from a single donor, a situation that offers advantages to the patient with regard to rejection reaction^{1,3}.

There is evidence of similar survival between heart-kidney transplanted cases and those with only heart transplantation, as well as in terms of rejection events⁴.

Our medical center, which has an experience of more than 20 years in solid organ transplantation, is pioneer in heart transplantation in Mexico⁵, which has enabled generating the development of knowledge, abilities and skills to consider the inclusion of heart-kidney combined transplantation as a therapeutic option. In addition, our center has extracorporeal kidney perfusion equipment available, which makes organ preservation feasible for 96 h. With these advantages, we

Correspondence:

*Guillermo Careaga-Reyna
Dirección General
Unidad Médica de Alta Especialidad
Hospital General Dr. Gaudencio González Garza
Centro Médico Nacional La Raza
Calzada Vallejo y Jacarandas, s/n
Col. La Raza, Del. Azcapotzalco
C.P. 02190, Ciudad de México, México
E-mail: gcareaga3@gmail.com

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have developed the combined heart and kidney transplantation program in two surgical stages to enable post-heart transplantation stabilization for the patient and, in appropriate conditions, carrying out the renal transplantation.

Below, we present our experience with this therapeutic modality.

Presentation of cases

Between January 1, 2011, and April 30, 2016, 766 kidney and 92 heart transplantations were carried out in our hospital center. In five of these cases, combined heart and kidney transplantation was performed in two stages, so that heart transplantation was initially carried out and, once the patient was stabilized, in a second stage, heterotopic renal transplantation was performed in the iliac fossa. The subjects involved were three males and two females with an average age of 25.6 years (range: 17-29 years).

Four organ procurements were at distance, i.e., outside the city, and one took place in our hospital center. For their protection, the organs were perfused with an HTK (histidine, tryptophan and ketoglutarate) solution and therein preserved during transportation.

The heart transplantation was orthotopic with bicaval technique in four cases and with Shumway classic technique (biatrial) in one. Surgical procedures were carried out under balanced general anesthesia.

For preservation of the kidney during the heart transplantation perioperative period, a renal hypothermic perfusion and preservation pump (Waters®) was used. Below, we present the cases.

Case 1

This is the case of 17-year old female with a history of chronic renal failure diagnosed in 2007, which warranted renal replacement therapy initiation with peritoneal dialysis. In 2008, she had a renal biopsy taken with histopathology result of endocapillary membranoproliferative glomerulonephritis with advanced chronic tubulointerstitial glomerular and vascular damage. The renal transplantation study protocol was initiated, but in 2009 she was hospitalized with data consistent with heart failure: dilated cardiomyopathy with mild pericardial effusion was found, which did not require emergency surgical management. The case was presented to the Cardiac and Renal Transplantation Clinic Medical-Surgical Board, which accepted it for heart-kidney transplantation. The patient was at New York Heart

Association (NYHA) functional class III. She had a weight of 33 kg and height of 1.52 m. Her blood type was O+. She had the following pre-transplantation clinical data: transthoracic echocardiogram (TTE): dilated cardiomyopathy, left ventricular ejection fraction (LVEF) of 25% and moderate pulmonary hypertension. Creatinine: 12.5 mg/dl; urea: 88 mg/dl; potassium: 5.4 mmol/l.

On April 5, 2011, the heart transplantation was carried out with biatrial technique, with total ischemia time of 4 h and 13 min and cardiopulmonary bypass time of 2 h and 3 min. On April 7, 2011, the cadaveric donor renal transplantation was performed, with total ischemia time of 60 h and 3 min and renal graft perfusion time of 51 h and 10 min, without complications. During the postoperative period, the patient displayed data consistent with malignant ischemic stroke in the territory of the left internal carotid of probable embolic origin; this was confirmed by CT scan and she received follow-up by the Clinical Neurology Department. On the following week there was blood flow gradual recovery as well as clinical recovery. The patient had postsurgical creatinine levels of 1.1 g/dl. She received immunosuppressant treatment based on prednisone, mycophenolate mofetil and tacrolimus. There was torpid evolution of the patient, with multiple complications, which required the following surgical interventions:

- Tracheostomy.
- Renal graft exploration with biopsy taking and ureteral reimplant due to a urinary fistula.
- Exploratory laparotomy due to acute abdomen; ileus intestinal ischemia was found, which required intestinal resection with ileostomy and mucosal fistula; an abscess was found in the pelvic cavity, which was drained; surgical cleansing was performed, and the peritoneal dialysis catheter was removed because it was placed onto the site of the abscess and 1000 cc of peritoneal reaction fluid were drained.
- Reintervention for ureteral reimplant due to urinary leak persistence; a 2-cm renal pelvis rupture was found, which was repaired.

The patient also had sepsis at different foci secondary to multiple germs, with *Escherichia coli*, enterococci and *Pseudomonas aeruginosa* standing out. She received specific antibiotic treatment according to the antibiogram. The patient experienced different cardiac hemodynamic alterations, which warranted inotropic treatment. Endomyocardial and renal graft biopsy showed no data consistent with rejection.

On June 12, 2011, the patient suffered a cardiac arrest secondary to septic shock, which was irreversible to resuscitation maneuvers.

Case 2

This is the case of a 28-year old woman with a history of end-stage renal disease secondary to pre-eclampsia suffered in 2007 that required renal replacement therapy with peritoneal dialysis since 2008; Tenckhoff catheter dysfunction occurred twice. Since 2010, the patient was undergoing hemodialysis twice weekly. She had heart failure secondary to dilated cardiomyopathy of uremic origin since 2011. She was at NHYA functional class III-IV. Blood type: O+. Height: 1.56 m; weight: 49 kg.

In January 2012 she entered the renal and heart transplantation study protocol. Pre-transplantation para-clinical studies: TTE: dilated cardiomyopathy with LVEF of 15% and severe mitral insufficiency. Mean pulmonary artery pressure (mPAP): 31 mmHg. Transpulmonary gradient (TPG): 11 mmHg. Pulmonary vascular resistance (PVR): 2.61 WU. Creatinine: 8.68 mg/dl; potassium: 6.2 mmol/l; urea: 84 mg/dl.

On July 14, 2012, orthotopic heart transplantation was carried out with bicaval technique, with ischemia total time of 225 min (3h and 45 min), 85-min (1 h and 25 min) aortic clamping and cardiopulmonary bypass time of 144 min (2 h and 24 min), without complications. On July 15, 2012, a cadaveric organ (organs from the same heart-kidney donor) renal transplantation was carried out, with ischemia time of 26 h and 25 min and perfusion time of 17 h and 5 min. The procedure presented no complications. The patient showed data consistent with acute rejection of the renal graft with decreased urinary volumes; she received endovenous steroid pulses and cyclosporine, with urination recovery and nitrogen compounds progressive drop, in addition to a second basiliximab dose. The patient had an adequate postsurgical evolution and was discharged from postsurgical therapy on July 23, 2012, and was discharged home with creatinine levels of 0.98 mg/dl and adequate function of the cardiac graft. On July 2013, she developed grade IB rejection of the cardiac graft, but responded adequately to steroid pulses. In 2014, the patient had a series of repeated urinary infections with mild elevation of nitrogen compounds and, therefore, she was started on a study protocol, which found a vesicoureteral reflux that was corrected with ureteral reimplant of the graft on November 26, 2014, with no complications. A biopsy of the

renal graft was taken as part of the study, with no data of rejection. Currently, the patient is managed with tacrolimus, mycophenolate mofetil and prednisone. Control creatinine: 1.1 mg/dl; cardiac biopsy with no data consistent with rejection and coronarography without chronic vasculopathy (October 29, 2014), with pulmonary artery trunk (PAT) pressure of 24 mmHg.

Case 3

This is the case of a 26-year old male patient with a history of chronic renal failure of undetermined origin since 2009, who received renal replacement therapy with peritoneal dialysis. There were no other relevant previous conditions. Blood type: A+. Height: 1.67 m. Weight: 58 kg. During the renal transplantation protocol implementation, the diagnosis of heart failure due to uremic dilated cardiomyopathy was added; the case was presented in the transplant session and was accepted for heart and kidney transplantation. Pre-transplantation paraclinical studies: left ventricle (LV) severe dysfunction, LVEF at 25%, severe mitral insufficiency and severe tricuspid insufficiency; mPAP: 24 mmHg; TPG: 6 mmHg; PVR: 2 WU. Creatinine: 16.27 mg/dl; urea: 114 mg/dl.

On May 6, 2014, an orthotopic heart transplantation procedure was carried out with bicaval technique; ischemia total time was 220 min (3 h and 40 min), aortic clamping time was 86 min (1 h and 24 min) and cardiopulmonary bypass time was 149 min (2 h and 29 min). On May 7, 2014, a cadaveric donor transplantation procedure was carried out, with cold ischemia time of 25 h and machine perfusion time of 17 h. In the postsurgical therapy postoperative period, diuresis was forced with diuretics and support with vasoactive amines. The patient was given an extra dose of basiliximab. Control echocardiograms showed slight LV dysfunction, which was treated with methylprednisolone pulses. The patient evolved favorably with adequate renal and cardiac function. During his stay at the hospitalization floor, left loculated pleural effusion was discovered and treated with a left pleurectomy procedure by means of left posterolateral thoracotomy, which had an adequate evolution. Tacrolimus and mycophenolate mofetil were used for immunosuppressant treatment. On May 20, 2015, was the last endomyocardial biopsy performed, as well as a coronarography, with PAT pressure of 100 mmHg and no data consistent with rejection or coronary lesion. Creatinine: 1.02 mg/dl; urea: 33 mg/dl; 24-h creatinine clearance: 58 ml/min/1.73 m².

Case 4

Twenty-nine year old man with a history of end-stage chronic renal failure since 2011 owing to bilateral renal hypoplasia, on renal replacement therapy since diagnosis with placement of three Tenckhoff catheters in 2011 and loss of useful cavity in 2012. Replacement therapy was initiated with hemodialysis 4 times per week. In 2012, a pericardial window procedure was practiced due to severe pericardial effusion. By the middle of 2014 he started experiencing dyspnea on exertion, asthenia and adynamia. A study protocol was applied, which found NYHS class III dilated cardiomyopathy to be associated. On October 2014, the case was presented and accepted at the session for kidney and heart transplantation. Blood type: O+; height: 1.62 m; weight: 56 kg. Pre-transplantation paraclinical studies: dilated cardiomyopathy, LVEF of 34%, generalized akinesia without thrombi. The viability assessment (echocardiogram/dobutamine) showed dilatation after volume load with paradoxical septal motion; mPAP: 21 mmHg; PVR: 2 WU. Creatinine: 6.5 mg/dl; urea: 58 mg/dl. On July 29, 2015, an orthotopic heart transplantation procedure was carried out with bicaval technique, ischemia total time of 270 min (4 h and 30 min), aortic partial clamping time of 105 min (1 h and 45 min) and cardiopulmonary bypass time of 169 min (2 h and 49 min). On July 30, 2015, a kidney transplantation procedure of the same cadaveric donor was carried out, with cold ischemia time of 23 h and 23 min and without complications. The patient evolved appropriately during the postsurgical period, with early airway extubation and vasoactive amine withdrawal. He was initiated on tacrolimus, mycophenolate mofetil and prednisone. At fourth day, he received a second basiliximab dose. At one month of transplantation, on September 2, 2015, an endomyocardial biopsy was obtained (PAT pressure: 14 mmHg), with no evidence of rejection (creatinine: 1.5 mg/dl; urea: 65 mg/dl).

Case 5

Twenty-eight-year old man. Blood type: O+. He worked as a messenger. He had a younger sister who received a kidney transplantation on December 2015 owing to chronic kidney disease (CKD) caused by glomerulonephritis. He suffered from CKD caused by glomerulonephritis of undetermined origin since 10 years ago, and was on the outpatient peritoneal dialysis program ever since. In the renal transplantation protocol, on an echocardiogram performed in January 2015,

uremic dilated cardiomyopathy with severe LV dysfunction and 20% LVEF was detected, which led to the patient not being accepted for renal transplantation. In February 2015, he was assessed by the Heart Transplantation Clinic, which corroborated the dilated cardiomyopathy, 20% LVEF and already-remodeled LV morphology (spherical), with LV diastolic diameter of 76 mm, mild mitral insufficiency and moderate PAH with PASP of 50 mmHg. Digoxin and sildenafil-based treatment was started, which helped to maintain the patient on NYHA functional class II-III.

In 2015, three months after treatment and fluid control optimization with peritoneal dialysis were started, a right catheterization was performed, with PAT pressure of 37/14 mmHg, mean pressure of 22 mmHg, TGP of 4 mmHg and PVR of 1 WU. With these data, the case was presented to the Heart Transplantation Committee, which accepted it for simultaneous heart and kidney transplantation.

On March 3, 2015, orthotopic heart transplantation from a multi-organ donor of our own hospital was carried out, with ischemia total time of 95 min, 70-min aortic clamping and 125-min cardiopulmonary bypass (CPB). Postoperative evolution was adequate, and the patient required minimal inotropic and vasopressor support, without hemorrhagic complications. In view of the cardiac evolution, on March 4, renal transplantation in the iliac fossa was carried out, with renal ischemia total time of 18 h. The renal graft started functioning since unclamping and reperfusion, with adequate urinary output generation and gradual decrease of nitrogen compounds. The patient was discharged home 12 days after the surgical procedures. On April 6, a cardiac biopsy was obtained with histopathology results indicating no rejection. Currently, nitrogen compounds are normal: serum creatinine of 1.2 mg/dl. Tacrolimus levels are 11 ng (normal). The cardiac graft has a LVEF of 65% and the renal graft is normal. The patient is at NYHA functional class I.

Discussion

End-stage heart failure is accompanied in many a case by renal failure, which can be secondary to low cardiac output in most patients who have it. However, there are patients in whom there is a kidney structural damage that causes renal failure.

In current epidemiological setting, with higher life expectancy and increased occurrence of non-transmittable chronic disease, for cases of heart failure secondary to ischemic or dilated cardiomyopathy and

renal failure secondary to diabetic nephropathy or chronic glomerulonephritis, it becomes necessary to consider treatment options that go beyond function-replacement therapies, such as dialysis in any of its modalities, or ventricular support for certain cases⁶.

In view of this scenario, ever since Norman et al.² presented in 1978 the first case where a combined heart-kidney transplantation was performed, this therapeutic modality has been increasingly used, and being applied in very selected cases⁷⁻⁹.

Surgical and organ protection and preservation techniques during procurement, transportation and implant on the receptor do not vary for none of the procedures. In our center, we have a perfusion machine available for renal preservation for up to 96 h outside the body and, in addition, we consider that combined transplantation is only necessary in cases of renal failure secondary to intrinsic kidney disease, but not in cases of hemodynamical renal failure, since as soon as cardiac output is improved, the renal function will gradually recover in the postoperative period, even if support with diuretics and even with dialysis is required perioperatively.

In our experience, we preferred to carry out the heart-kidney transplantation simultaneously, even when an operative mortality of up to 21% is referred⁸⁻¹⁰, since we considered that the fact of organs coming from a single donor decreases the possibilities of rejection. In addition, immunomodulation of the receptor by simultaneous transplantation has also been considered, or introduction of hematopoietic elements that have allowed for less vasculopathy in the heart and lower incidence of renal rejection to be observed in heart-kidney transplanted patients than in those with heart or kidney separately transplanted¹¹. Mid- and long-term patient survival is quite acceptable¹². Obviously, we shouldn't forget the risk for infections associated with immunosuppressant therapy, as in the case reported by Tobón et al.¹³ of amphotericin B therapy-refractory mucormycosis that was treated with posaconazole, which forces a very careful follow-up of patients to be carried out and for them to adhere to care and treatment measures they are indicated.

Bacchi et al. present a very similar variety of cases by informing about one case per year in their 2003 to 2009 series, with similar results in survival, although with older patients than in our experience¹⁴.

Based on the above, we can conclude that heart-kidney combined transplantation is a treatment option for selected cases, with improvement in survival and quality of life of recipients, without failing to mention that, according to available data, our hospital center is the only one in Mexico that performs this type of procedures.

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