Simultaneous heart and kidney transplantation from a single donor

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Abstract

Objective: There are no guidelines to establish the indications and contraindications for a simultaneous heart and kidney transplantation. We report our single-institutional experience with simultaneous heart and kidney transplantation.

Methods: Retrospective chart review.

Results: Between 1995 and 2006, 13 patients with co-existing end-stage heart and renal failure underwent simultaneous heart and kidney transplantation at the authors’ hospital. Heart failure was secondary to dilated cardiomyopathy in five patients, ischemic cardiomyopathy in three, cardiac allograft vasculopathy in two, and congenital heart disease, cardiac allograft failure, and acute myocarditis each in one. Renal failure was secondary to glomerulonephritis in six patients, heart failure in two, cyclosporine nephroathy in three, hypertension in one, and systemic lupus erythematosus in one. Eight patients were in UNOS status IA and five patients in UNOS status II before transplantation. The 30-day mortality rate and in-hospital mortality rate were 15% and 38%. Of eight patients in UNOS status IA, seven patients have lived beyond 30 days and three (38%) beyond 1 year. Of five patients in UNOS status II, four patients have lived beyond 30 days and four (80%) beyond 1 year. Patients in UNOS status IA had high rates of previous cardiac surgery, cardiac allograft rejection, and major renal allograft complications.

Conclusions: Although simultaneous heart and kidney transplantation continues to be a viable option for patients with co-existing end-stage heart and renal failure, the results do not match those of isolated heart transplantation. The clinical outcomes were not satisfactory in UNOS status IA patients with previous cardiac surgery.

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Keywords: Dual organ transplantation; Heart transplantation; Kidney transplantation; Outcome

1. Introduction

In isolated heart transplantation, preoperative renal failure is one of the major risk factors for mortality [1]. In select patients with co-existing end-stage heart and renal failure, simultaneous heart and kidney transplantation with allograft from a single donor proved to have satisfactory short-term and long-term results [2–13]. Simultaneous heart and kidney transplantation has therefore become an accepted therapeutic option for patients with end-stage heart failure associated with severely impaired renal function. However, there are no guidelines at this moment to establish the indications and contraindications for a simultaneous heart and kidney transplantation. Here, we report our single-institutional experience with simultaneous heart and kidney transplantation.

2. Patients and methods

2.1. Patients

A total of 265 consecutive patients underwent heart transplantation from June 1995 to October 2006 at the National Taiwan University Hospital. Patients undergoing simultaneous heart and kidney transplantation from a single donor were included in this study. These patients, affected by end-stage heart failure, had severe renal failure when listed for heart transplantation. Combined heart and kidney transplantation were performed with allografts harvested from a single donor. Donors were matched for each recipient on the basis of donor and recipient ABO blood group identity and donor/recipient body weight ratio ≥ 0.8.

Data on age, sex, diagnosis of heart disease and renal disease, cardiac and renal allograft ischemic time, cardiopulmonary bypass time, renal and liver function tests before transplantation, and clinical outcomes were recorded.

2.2. Heart transplantation

All of the procedures of heart transplantation were performed through a median sternotomy.
Heart and kidney harvesting, preservation, and grafting were performed according to the routine technique. Orthotopic heart transplantation was performed first in all cases. After hemodynamic stability and hemostasis were achieved, the chest was closed, and kidney transplantation was then performed without delay in standard fashion.

Postoperative management in intensive care unit was the same as that in routine patients receiving isolated heart transplantation. Blood components were given whenever needed and no aprotinin was used in our patients. Major postoperative complications were neurological (consciousness disturbance, seizure or stroke), pulmonary (prolonged ventilator support for more than 48 h), infectious (wound infection, bacteremia, pneumonia, or urinary tract infection), gastrointestinal, renal (acute renal failure or need of new dialysis), bleeding (profuse chest tube drainage in need of reoperation), and hepatic decompensation (hepatic function deterioration or hepatic failure).

2.3. Immunosuppression

All patients received triple-drug immunosuppressive therapy according to our heart transplantation protocol as previously described [14]. We used rabbit antithymocyte globulins for induction therapy. Azathioprine (4 mg/kg) was given 1 h before the operation. Solumedrol (1000 mg) was infused during release of the aortic cross-clamp. Rabbit antithymocyte globulin (1.5—2.5 mg/kg/day) was given after transplantation for 5 days. Cyclosporine was started orally within 5 days after transplantation or after the recovery of renal function. Cyclosporine dose was adjusted according to renal function and serum cyclosporine level, which was maintained at the trough level of 300—500 ng/ml during the first three months after transplantation and 200—300 ng/ml 1 year after transplantation. Azathioprine was given at 1—2 mg/kg/day after transplantation, with the dose adjusted to maintain a white blood cell count 4000—6000/mm³. Prednisone (0.5 mg/kg/day) was started on the second postoperative day and tapered to 0.2 mg/kg/day by the first month after transplantation. Tacrolimus and mycophenolate mofetil were used for recurrent cardiac allograft rejection or severe adverse reactions to cyclosporine and azathioprine. Since 2004, we started to use mycophenolate mofetil for primary immunosuppression instead of azathioprine. To prevent nephrotoxicity, cyclosporine dose was decreased to maintain serum trough level of 250—350 ng/ml during the first three months after transplantation and 150—250 ng/ml 1 year after transplantation.

All patients were followed monthly at a special cardiac transplant clinic. Standard chest roentgenogram, blood tests, electrocardiogram and physical examinations were routinely performed at regular intervals.

Endomyocardial biopsy was performed weekly in the first month, biweekly in the second month, monthly in the 6 months and yearly 6 months after transplantation. For those patients surviving for more than 6 months after transplantation, coronary angiography was performed annually for surveillance of cardiac allograft vasculopathy. The kidney allograft was followed with serial determination of serum blood urea nitrogen and serum creatinine. Needle biopsy of the kidney allograft was undertaken only if there was an elevation in serum creatinine over baseline that did not respond to standard treatment.

Perioperative prophylactic antibiotics included 1 g of cefazolin given intravenously to recipients every 8 h until removal of endotracheal tube and drain tubes. In an attempt to prevent oropharyngeal candidiasis, mycostatin suspension (5 cc, ‘swish and swallow’) was given orally four times a day for 1 month after transplantation. Acyclovir 200 mg every 6 h was used for prophylaxis against herpes simplex virus and varicella zoster virus for 1 month after transplantation.

2.4. Statistical analysis

Patient survival in simultaneous heart and kidney transplantation patients was compared with the survival in isolated heart transplantation patients. Survival curve was plotted by the Kaplan—Meier method. Survival was compared by log-rank test. A p value ≤0.05 was considered statistically significant.

3. Results

3.1. Patients

Of the 265 patients undergoing heart transplantation, 13 patients (5%) underwent simultaneous heart and kidney transplantation. Patient characteristics are summarized in Table 1. End-stage heart failure was secondary to dilated cardiomyopathy in five patients (42%), ischemic cardiomyopathy in three (25%), cardiac allograft vasculopathy in two, and congenital heart disease, non-diagnostic cardiac allograft failure, and acute myocarditis each in one. In six patients (46%), a previous cardiac surgery was recorded.

Three patients with cardiac allograft failure were treated with immunosuppressants before they underwent combined heart and kidney transplantation. Eight patients were in the United Network for Organ Sharing (UNOS) status IA and five patients in UNOS status II before transplantation. Six patients had endotracheal intubation and mechanical ventilation before transplantation. Mechanical circulatory support was required in four patients before transplantation.

Renal failure was secondary to glomerulonephritis in six patients, heart failure in two, cyclosporine nephropathy in three, hypertension in one, and systemic lupus erythematosus in one. Ten patients (83%) had chronic irreversible end-stage renal failure.

Eleven donors were male with median age of 40 years (range, 17—62). Donor profiles are summarized in Table 2. The median duration of ischemic time was 124 min (range, 91—210) for the cardiac allograft and 6 h (range, 6—8) for the kidney allograft.

3.2. Hospital outcome

The hospital outcome and postoperative complications are summarized in Table 2. Patient no. 3 died after 1 day of surgical bleeding. Bloodstream infection occurred in five patients and it led to four hospital mortalities. The causing pathogens were Pseudomonas aeruginosa and Enterococcus faecalis (patient no. 8), Enterobacter cloacae, Acinetobacter
and *Chryseobacterium meningosepticum* (patient no. 10), *Enterococcus faecalis* (patient no. 11), *Enterobacter cloaca* (patient no. 12), and *Stenotrophomonas maltophilia* and *Acinetobacter baumannii* (patient no. 7) each in one patient. Overall, the 30-day mortality rate and in-hospital mortality rate in our series were 15% (2/13) and 38% (5/13).

Immediate diuresis from the transplant kidney started in 10 patients. Renal function gradually normalized, with serum creatinine ranging from 0.5 to 3.0 mg/dl at 1 month after kidney transplantation (Table 2). Patient no. 10 and no. 13 did not recover autonomous renal function immediately after kidney transplantation, and underwent regular dialysis treatment after transplantation. Patient no. 10 underwent donor nephrectomy because of renal allograft infection and persistent bacteremia.

### 3.3. Cardiac complications

Two patients showed a single episode of acute cardiac rejection on endomyocardial biopsy, International Society of Heart Lung Transplantation (ISHLT) Grade 3A in patient 6 after 7 months and ISHLT Grade 2 patient 11 after 3 months. All rejection episodes responded to therapy with methylprednisolone 1000 mg intravenously on 3 consecutive days.
and addition of sirolimus. None of our patients had coronary allograft vasculopathy.

Patient no. 6, a case of retransplantation, died of non-diagnostic cardiac allograft failure 11 months after transplantation. Patient no. 9 died suddenly at home 15 months after transplantation. The cardiac function remained normal in long-term surviving patients; all patients are New York Heart Association Functional Class I or II.

3.4. Renal complications

Major renal allograft complications have been primary nonfunctioning grafts in two patients, acute cellular rejection in two patients, and crescentic glomerulonephritis in one patient (Table 3). Patient no. 10 and no. 13 did not recover autonomous renal function immediately after kidney transplantation because of renal vascular thrombosis. Patient no. 7, a case of retransplantation, had heavy proteinuria and hypoalbuminemia 2 months after transplantation. Renal biopsy showed crescentic glomerulonephritis, which responded well to a course of plasmapheresis. Patient no. 9 had acute cellular rejection of renal allograft (Banff Classification IB) 9 months after transplantation. Patient no. 11 had simultaneous acute cellular rejection of cardiac and renal allograft (Banff Classification IIA) 3 months after transplantation. Her native kidney function recovered gradually. All rejection episodes responded to therapy with methylprednisolone 1000 mg intravenously on 3 consecutive days and modification of maintenance immunosuppression. Five surviving patients have functioning kidney allografts with a follow-up duration ranging from 20 to 146 months; the serum creatinine in the surviving patients ranged from 1.1 to 2.2 mg/dl at the last follow-up outpatient visit (Table 3).

3.5. Late outcome

Follow-up was complete in all patients. Among eight discharged patients, there were three late mortalities (Table 3). Major non-lethal late complications were acute cardiac allograft rejection in two patients, cytomegalovirus infection in two, diabetes mellitus in two, pneumonia caused by Klebsiella pneumoniae, and pacemaker implantation in one (Table 3).

The mortality rates of simultaneous heart and kidney transplantation led to an overall Kaplan–Meier survival of 84.6% ± 10.0% at 30 days, 53.9% ± 13.8% at 1 year, and 46.2 ± 13.8% at 3 years, and 50.0 ± 16.5% at 5 years. These results do not match with our survival in isolated heart transplantation patients, that is, 92.9% ± 1.6% at 30 days, 83.7% ± 2.3% at 1 year, and 70.9% ± 3.0% at 3 years. However, because of the smallness of case numbers, there was no significant statistical difference (p = 0.1025 by log-rank test).

3.6. UNOS status

The impact of UNOS status is shown in Table 4. Of eight patients in UNOS status IA before transplantation, six patients had previous cardiac surgery, but none of five patients in UNOS status II had it. Of eight patients in UNOS status IA before transplantation, seven patients have lived beyond 30 days but only three (38%) beyond 1 year. Of five

<table>
<thead>
<tr>
<th>Variables</th>
<th>UNOS IA</th>
<th>UNOS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplant &lt; 50 years</td>
<td>50% (4/8)</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>75% (6/8)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Diagnosis of dilated cardiomyopathy</td>
<td>0% (0/8)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td>30-day survival</td>
<td>88% (7/8)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>1-year survival</td>
<td>38% (3/8)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>Acute cardiac allograft rejection in survivors beyond 7 days</td>
<td>29% (2/7)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Major renal allograft complications in survivors beyond 7 days</td>
<td>57% (4/7)</td>
<td>20% (1/5)</td>
</tr>
</tbody>
</table>
patients in UNOS status II before transplantation, four patients have lived beyond 30 days and four (80%) beyond 1 year. Renal complications occurred in four of seven UNOS status IA patients who survived beyond 7 days. However, renal complications occurred in none of five UNOS status II patients who survived beyond 7 days. Acute cardiac allograft rejection occurred in two of seven UNOS status IA patients who survived beyond 7 days. However, acute cardiac allograft rejection occurred in one of five UNOS status II patients who survived beyond 7 days.

4. Discussion

Recipients of isolated heart transplants are at risk for acute renal failure resulting from a combination of preoperative renal insufficiency, postcardiotomy heart failure, effects of cardiopulmonary bypass and nephrotoxic effects of immunosuppression. Acute renal failure requiring renal replacement therapy was associated with increased mortality after heart transplantation [15]. In fact, advanced renal disease is a formal contraindication to heart transplantation, and heart failure may make a patient ineligible for kidney transplantation. In end-stage heart failure where concomitant renal failure is a contraindication for heart transplantation, simultaneous heart and kidney transplantation may be the only feasible therapeutic option. The number of simultaneous heart and kidney transplantations increases every year, and the International Society of Heart and Lung Transplantation has reported simultaneous heart and kidney transplantations with survival rates of 92% at 30 days, 76% at 1 year, and 67% at 2 years [12]. In this current series, we further demonstrated a poor survival of simultaneous heart and kidney transplantation in those patients in UNOS status IA before transplantation. All patients in UNOS status II had dilated cardiomyopathy as indication for heart transplantation and had good clinical outcome. Six of the eight patients in UNOS status IA suffered from coronary artery disease or cardiac allograft vasculopathy and had poor outcome.

Compared with isolated heart transplantation, simultaneous heart and kidney transplantation does not adversely affect short-term and long-term survival and results in a lower incidence of treated cardiac allograft rejection [2–13]. Recipients of simultaneous heart and kidney transplantations from a single donor have less acute rejection of the heart and the kidney allograft compared with isolated heart or kidney transplant recipients. Simultaneous rejection of both organs is very uncommon [2–13,16]. Cardiac allograft vasculopathy is also decreased significantly when cardiac transplantation is combined with a kidney allograft [17]. These phenomena may result from immune modulation of the recipient by simultaneous transplant of disparate tissues or introduction of immune-modulating hematopoietic elements [16]. These findings suggest that simultaneous heart and kidney transplantation may be an acceptable option in a small subset of potential heart transplant recipients with severe renal dysfunction. Given the good results of simultaneous heart and kidney transplantation reported in the literature, the indications have expanded and contraindications have diminished. However, there are no guidelines at this moment to establish the indications and contraindications for a simultaneous heart and kidney transplantation. It is unclear whether patients with heart failure and renal insufficiency should receive a simultaneous heart and kidney transplant or whether isolated heart transplantation is sufficient to restore native renal function. It is suggested that a simultaneous heart and kidney transplantation is necessary in patients with cardiomyopathy and renal insufficiency due to primary kidney disease, but not in those with hemodynamically mediated renal failure [7]. Also it is unclear whether patients with preoperative refractory shock should receive a simultaneous heart and kidney transplant.

In this current series, the survival rate of simultaneous heart and kidney transplantation did not match those of isolated heart transplantation, and the rate of major renal allograft complications in UNOS status IA patients was high. Furthermore, we demonstrated a high rate of cardiac allograft rejection and major renal allograft complications in UNOS status IA patients. The poor results in this study were probably a result of the inclusion of two patients with retransplantation, six patients with previous cardiac surgery, and seven patients in UNOS status IA. There were two reasons. First, aggressive perioperative volume expansion is recommended to maximize functional recovery of a kidney allograft, but patients with a complication of post-transplant heart failure are exposed to the risk of fluid overload, acute respiratory failure, prolonged ventilation and then mortality after transplantation. In this situation, the ischemic renal graft is exposed to low perfusion pressure and high doses of vasoconstrictive drugs after transplantation. It may subsequently lead to renal allograft dysfunction, rejection, and even graft loss [18,19]. Second, elevated pretransplant panel-reactive antibody remains a significant risk factor of mortality and graft loss in heart transplant or renal transplant recipients. And the development of panel-reactive antibody may occur as a result of previous blood transfusions, previous pregnancies, and previous transplantation [20].

In this current series, the rates of perioperative mortality and renal allograft complications increased after 2004. It coincided with the time when mycophenolate mofetil was introduced in our immunosuppressive regimen. Mycophenolate mofetil has been demonstrated to both decreased acute rejection and improved graft survival in renal transplant recipients [21]. But it is not conclusive [22]. Further studies are needed.

4.1. Study limitation

This study was limited by small case numbers, retrospective study, lack of control group and a short duration of follow-up. This study is one of the largest series of simultaneous heart and kidney transplantation in patients with co-existing end-stage heart and renal failure.

Previous reports in patients with azotemia suggested a serum creatinine >2 mg/dl [23] or glomerular filtration rate <30 ml/min as an indication for simultaneous heart and kidney transplantation. In this current series, our data showed that a simultaneous heart and kidney transplantation could be performed in UNOS status II patients with co-existing heart and renal failure, but not in UNOS status IA patients. Our results were preliminary. A careful multi-center study is needed to establish guidelines of what UNOS status IA
patients with preoperative azotemia warrants a simultaneous heart and kidney transplantation.

4.2. Conclusions

Although simultaneous heart and kidney transplantation continues to be a viable option for patients with co-existing heart and renal failure, the results do not match those of isolated heart transplantation. The clinical outcomes were not satisfactory in UNOS status IA patients with previous cardiac surgery.

References


