

Kidney Transplantation from a Donor Following Cardiac Death Supported with Extracorporeal Membrane Oxygenation

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To expand the donor pool, organ donation after cardiac death (DCD) has emerged. However, kidneys from DCD donors have a period of long warm ischemia between cardiac arrest and the harvesting of the organs. Recently, we used extracorporeal membrane oxygenation (ECMO) to minimize ischemic injury during 'no touch' periods in a Maastricht category II DCD donor and performed two successful kidney transplantations. The kidneys were procured from a 49-yr-old male donor. The warm ischemia time was 31 min, and the time of maintained circulation using ECMO was 7 hr 55 min. The cold ischemia time was 9 hr 15 min. The kidneys were transplanted into two recipients and functioned immediately after reperfusion. The grafts showed excellent function at one and three months post-transplantation; serum creatinine (SCr) levels were 1.0 mg/dL and 0.8 mg/dL and the estimated glomerular filtration rates (eGFR) were 63 mL/min/1.73 m² and 78 mL/min/1.73 m² in the first recipient, and SCr levels were 1.1 mg/dL and 1.0 mg/dL and eGFR were 56 mL/min/1.73 m² and 64 mL/min/1.73 m² in the second recipient. In conclusion, it is suggested that kidney transplantation from a category II DCD donor assisted by ECMO is a reasonable modality for expanding donor pool.

Key Words: Extracorporeal Membrane Oxygenation; Kidney Transplantation; Organ Donation After Cardiac Death

INTRODUCTION

Kidney transplantation has become an effective means of treating end-stage renal disease (ESRD), but the shortage of eligible organs limits its clinical application and is now a major problem for transplantation worldwide. Despite a social/legal consensus regarding brain death since February 2000 in Korea, the number of patients waiting for kidney transplantation continues growing dramatically, and the shortage of donation after brain death (DBD) still remains a major problem. Despite active donor actions and attempts to increase living donors using extended criteria or exchange donors, the discrepancy between the number of available kidneys for transplantation and the number of patients awaiting transplantation has been widening. At the end of 2010, the Korean Organization Network for Organ Sharing (KONOS) national waiting list for kidney transplantation was approaching 9,294 patients, whereas only 1,223 kidney transplantations were performed in a year, including 479 transplants from DBD donors in 2009 (1). The mean waiting time for kidney transplantation from a deceased donor was 1,299 days in Korea, varying on the degree of HLA mis-matching and blood type (1).

To expand the donor pool, organ donation after cardiac death

(DCD) has been recently started in many countries, including Korea (2-5). However, kidneys from DCD donors retain a long period of warm ischemia between the cardio-circulatory arrest of donors and cold preservation of the donated organs. The warm ischemic damage during this period might lead the grafts to primary non-function or delayed graft function. The suitability of a donor's organs for transplantation declines rapidly during the warm ischemic condition after cardiac death. Transplantation surgeons are reluctant to use organs rescued from cardiac arrested donors due to the threat of primary graft non-function related to prolonged warm ischemia time. To prevent or minimize the warm ischemic damage on the donated organs, it is necessary to make the warm ischemic time very short or to perfuse oxygenated blood into the donor organ, even after cardiac arrest, until organ procurement. Kidneys from DCD donors require additional support during preservation to maintain tissue viability.

Uncontrolled DCD donors are those who have had an unexpected cardiopulmonary arrest or for whom cardiopulmonary resuscitation has been unsuccessful (Maastricht I, II). The use of veno-arterial extracorporeal membrane oxygenation (ECMO) after cardiac arrest restores the flow of warm oxygenated blood during the interval between death and organ procurement.

ECMO, a proven technology that can provide the normal perfusion of oxygenated blood into organs in the absence of cardiac activity, has the potential to maintain organ quality even after cessation of cardiac circulation in uncontrolled DCD donors. The use of ECMO after cardiac death in order to maintain sufficient oxygenation of potential donor organs has been reported in several studies (6-9). Those protocols introduce ECMO support immediately after death declaration through arterial and venous catheters that are inserted before death is declared. ECMO improved outcomes in transplanted kidneys, livers, and pancreas from DCD donors because of improved organ perfusion and oxygenation before organ recovery. By maintaining the flow of oxygenated blood to the organs to the moment of recovery and thereby reducing warm ischemic time, ECMO improved the viability of donor organ function in a way similar to organs recovered from a brain-dead donor with a beating heart. That improvement in recovered organs permitted an expansion of the potential organ donor pool by 33% (7).

In the first case of its kind in Korea, we recently used ECMO to minimize ischemic injury during the 'no touch' periods of a Maastricht category II DCD donor and performed two successful kidney transplantations from the donor.

MATERIALS AND METHODS

Study design

We retrospectively reviewed the medical records of DCD donors and 2 kidney transplant recipients. Medical conditions of the donor and procedures that might be related during processing of organ donation were recorded. Pre- and post-transplantation medical conditions of the two recipients and their graft functions were also monitored. Recipients' serum creatinine (SCr) and body weight were measured on a daily basis until two weeks post-transplantation and were then measured weekly. We used the SCr and estimated glomerular filtration rate (eGFR) as a parameter of the donor's kidney function before organ recovery and recipients' graft function after transplantation. The donor's eGFR and recipients' eGFR at one and three months post-transplantation were calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) formula of Levey et al. (10): $eGFR (mL/min/1.73 m^3) = 175 \times SCr^{-1.154} \times (Age)^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if African American).

The warm ischemia time was defined as the time between the cessation of cardio-circulatory activity and the initiation of ECMO support, and the cold ischemia time was defined as the time between aortic cross-clamp with cold perfusion in the donor and kidney revascularization in the recipient.

Donor management before and during organ preservation

Careful physical examination and history taking from the family were obtained. Vital signs, including blood pressure, pulse rate

and rhythm, respiratory rate, and trans-cutaneous oxygen saturation, were monitored. Either inotropics such as norepinephrine and dopamine were administered to stabilize vital signs, and vasopressin was given to control diabetes insipidus.

An ECMO device was applied to minimize warm ischemic injury of the kidneys following declaration of cardiac death. After initiation of ECMO, the donor was transported to the operating room, where organs were procured using techniques similar to those for donation after brain death donors. As soon as the organs were perfused with cold preserved histidine-tryptophan-ketoglutarate (HTK) solution via a femoral arterial catheter used for ECMO, we clamped the donor's descending aorta to enable the preservation solution to flow effectively into intra-abdominal organs. After organ recovery from the donor, the kidneys were biopsied for frozen section.

Kidney allocation

Kidneys were allocated by the KONOS according to the guidelines, referring to donor information such as age, human leukocyte antigen (HLA), ABO blood type, history of hypertension and diabetes, cause of death, serum creatinine, urine output, and laboratory results for transmittable diseases.

Immunosuppression

Immunosuppression consisted of tacrolimus, corticosteroids, and mycophenolate mofetil. Tacrolimus was given orally at a dose of 0.2 mg/kg/day, starting just before transplantation. Within a month after transplantation, the dose of the drug was individually adjusted, with a goal trough blood level between 10 ng/mL and 15 ng/mL. Target blood trough levels of tacrolimus were reduced to between 7 ng/mL and 10 ng/mL after one month post-transplantation. Methylprednisolone was injected at the following doses: 500 mg on the day of operation, and 250 mg, 125 mg, and 60 mg on post-operative days 1, 2, and 3, respectively. Prednisolone was given at an oral dose of 30 mg/day starting on post-operative day 4, then slowly tapered to a maintenance dose of 10 mg/day. For both recipients, basilixumab 20 mg was given intravenously just prior to transplant and four days after transplantation.

Transplantation surgery

The kidney transplantation was performed in the usual manner. Both kidneys were transplanted to the right common iliac artery and vein. The ureters were implanted in bladders using Lich-Gregoir's methods. The transplant surgical procedures were simultaneously performed by two experienced surgeons.

Ethics Statements

This single center retrospective study has been approved by institutional review board of Ajou University School of Medicine (IRB No.: AJRB-MED-OBS-11-219). The family members of the

donor gave their informed consent for organ donation after cardiac death before ECMO device application. The two recipients were fully informed about kidney transplantation using the kidneys from DCD donor and gave their written consents prior to surgery.

RESULTS

Cardiac death and organ recovery from the donor

A 49-yr-old male patient with a traumatic subdural hematoma following emergency craniotomy and temporal lobectomy was referred to our transplant center. Informed consent for organ donation was taken from the family. Medical or social history such as hypertension, diabetes, viral hepatitis, and drugs/alcohol consumption was negative. His vital signs, including blood pressure and pulse rate, were unstable. Even though the GCS (Glasgow coma scale) was 5, the clinical findings did not meet the criteria of brain death, because he had a self-respiratory drive and minor motor activity. On the 15th day after the cranial surgery, cardiac arrest occurred. Intensive cardiopulmonary resuscitation for 40 min turned out to be unsuccessful. The ECMO device started running at 31 min after declaration of cardiac death and was maintained for 7 hr 55 min until the organ was preserved with cold HTK solution. The cold ischemic times of each kidney were 9 hr 15 min and 9 hr 25 min until re-perfusion of the recipient's blood into the kidney graft was established.

His renal function was well preserved until cardiac arrest. The initial serum creatinine level and eGFR were 0.8 mg/dL and 109 mL/min/1.73 m², respectively, with adequate urine amount. After cardiac arrest, those values deteriorated to 1.6 mg/dL and 49 mL/min/1.73 m², respectively, with trivial urine output while the ECMO running.

Each kidney had one renal artery and one renal vein; the right kidney weighed 285.4 g, and the left kidney weighed 269.5 g. They were easily perfused with HTK preservation solution during the bench procedure without an intra-parenchymal vascular resistance. Time zero biopsy for frozen section, done during a bench procedure immediately after organ recovery, revealed no glomerular abnormality but was suspicious for acute tubular necrosis without overt necrosis.

Recipient selection

The first recipient, a 59-yr-old female, had been on peritoneal dialysis for 20 yr. She had 4 HLA antigens mis-matched, and negative lymphocyte cross matching to the donor. She had no history of diabetes mellitus and was only on anti-hypertensives. Preoperative assessment showed no serologic evidence for viral infection such as HIV and hepatitis B and C. She had been waiting for kidney transplantation for 1,596 days.

The second recipient, a 43-yr-old female, had been on hemodialysis for 6 yr. She had hypertension and diabetes mellitus,

controlled with oral hypoglycemic medication and insulin. Five HLA antigens were mis-matched, and lymphocyte cross matching was negative to the donor. There was no serological evidence of HIV and hepatitis B and C. She had been waiting for kidney transplantation for 1,708 days.

Graft kidney function after the transplantation

The kidney grafts functioned immediately after reperfusion and made urine. The first recipient had 250-400 mL/hr of urine output immediately post-transplantation that was adequately maintained. The SCr level was 8.6 mg/dL immediately post-transplantation and steadily decreased to 1.4 mg/dL at seven days after the transplantation. On the Doppler ultrasonography at seven days post-transplantation, the implanted kidney showed normal contour without evidence of perfusion defect and resistive indices between 0.66 and 0.69. She was home on day 10 post-transplantation. At a month post-transplantation, the recipient's 24-hr urine was collected for the amount of urine output (1,870 mL), creatinine excretion (910.7 mg), proteinuria (0 mg), and creatinine clearance calculation (62.0 mL/min/BSA). At one and three months post-transplantation, the SCr levels were 1.0 mg/dL and 0.8 mg/dL, and the eGFR were 63 mL/min/1.73 m² and 78 mL/min/1.73 m², respectively.

The second recipient also had 250-500 mL/hr of urine output immediately post-transplantation that decreased to 30-40 mL/hr three days post-transplantation. Restriction of water intake was required for the following two days until recovery from the oliguric phase, and the urine output increased to 1,700 mL/day on day 7 post-transplantation. The SCr level was 7.8 mg/dL immediately post-transplantation and during the oliguric phase and then slowly decreased to 2.4 mg/dL on day 7 post-transplantation. Doppler ultrasonography for the implanted kidney at day 7 post-transplantation showed normal ranges of resistive indices, between 0.61 and 0.68, without evidence of perfusion defect. At a month post-transplantation, the recipient's 24-hr urine was also collected for the amount of urine output (2,750 mL), creatinine excretion (962.5 mg), proteinuria (0 mg), and creatinine clearance calculation (56.2 mL/min/BSA). At one and three months post-transplantation, the SCr levels were 1.1 mg/dL and 1.0 mg/dL, and the eGFR were 56 mL/min/1.73 m² and 64 mL/min/1.73 m², respectively.

DISCUSSION

DCD is now becoming an accepted medical practice in many countries following a period during which the procedure was practically abandoned because of poor results with organs transplanted from those donors. In Korea, organ transplantation from a DCD donor is now emerging, and the clinical outcome of a DCD program has been recently reported in Korea (3). Outcomes after DCD kidney transplantation have been

previously described to be inferior to DBD kidney transplantation (11, 12), because DCD kidneys inevitably sustain a longer period of warm ischemia than DBD. The first international workshop on DCD donation in Maastricht in 1995 classified four categories in accordance with the length of the time period of warm ischemia (13). In particular, uncontrolled donors such as category I and II donors have a long warm ischemia time.

To reduce that damage, rapid cooling of the organs is indicated. In many centers, in-situ preservation (ISP) is the method of choice for uncontrolled DCD donors, Maastricht category I and II (14, 15). However, Snoeijs et al. (16) reported 23.3% of failure to kidney transplantation combined with technical complications of ISP, such as impossible catheter insertion, poor flush out, using a pediatric catheter, and catheter balloon rupture. A prolonged catheter insertion time is associated with poor transplant outcome, which not only depends on the longer warm ischemia time but also on the quality of the arterial tract.

ECMO is a device that provides temporary circulation support and systemic oxygenation for patients with reversible respiratory failure that cannot be adequately supported with conventional mechanical ventilation and inotropic support (17), and it has been accepted in organ preservation methods for DCD donors. Maintaining circulation before retrieval, continuously during the preservation period, or for a short period to resuscitate the kidney appears to be advantageous compared to hypothermic techniques such as ISP. Furthermore, normothermic preservation techniques may be used as a method to protect against preservation and ischemia/reperfusion injury, resuscitate the kidney to instigate repair mechanisms, and also allow a comprehensive assessment of the kidney before it is transplanted. Objective kidney graft quality assessment is a prerequisite to safely expand the donor pool without compromising results. Assessment of kidney viability before transplantation may be particularly advantageous for extended criteria or DCD donor kidneys to prevent the transplantation of non-functioning kidneys. Normothermic perfusion could offer a more accurate and immediate assessment of viability compared to hypothermic techniques (18).

In Spain, there has been a long period of experience with the use of ECMO in category I and II DCD donors (9, 19, 20). Using that technique, the results of DCD kidney transplantation were equivalent to DBD transplantation, with 1-yr and 5-yr graft survival rates of 87.4% and 82.1%, respectively (21). In this study, the clinical course and graft function of two recipients were similar to those of kidney transplantation from DBD donors in our center (data not shown).

In Korea, organ allocation is controlled by a national transplantation organization, called KONOS, rather than a regional organ procurement organization. Usually, the organ allocation is initiated after issuing the reports of the HLA typing of donors. An additional long period of time was required for evaluation of

recipients' medical status, including the result of lymphocyte cross-matching. For those reasons, we spent a long supported circulation time using ECMO and cold ischemia time after procurement of kidneys. Under the present conditions, many potential DCD donors, especially Maastricht category I and II uncontrolled donors, would be abandoned. To expand donor organ pool, aggressive but careful clinical approaching was recommended for DCD donors even in Maastricht category II donors (22). Fortunately, despite a long preparation time for organ allocation, evaluation of recipients, and lymphocyte cross-matching, hemodynamic circulation supported with ECMO allowed the donated kidney to be well preserved and gave excellent graft function after transplantation in this case.

In conclusion, our experience showed that kidney transplantation from a category II DCD donor assisted by ECMO is a reasonable modality for expanding the donor pool. ECMO assisted organ preservation of DCD donors could improve renal graft outcomes after transplantation.

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