Four-Year Experience With Extracorporeal Membrane Oxygenation for Kidney Transplant Patients With Severe Refractory Cardiopulmonary Insufficiency

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ABSTRACT

Background. Kidney transplant (KT) recipients are vulnerable to infections because of their immunosuppressive treatments, and they occasionally exhibit serious acute cardiopulmonary dysfunction. The purpose of this study was to report the clinical outcomes of using extracorporeal membrane oxygenation (ECMO) in KT recipients and to identify risk factors for ECMO weaning failure.

Methods. We retrospectively reviewed the electronic medical records of KT patients who experienced severe cardiopulmonary dysfunction refractory to conventional therapy and received ECMO at the Asan Medical Center Surgical Intensive Care Unit between December 2010 and December 2014.

Results. During the 4-year study period, 12 KT patients required ECMO management. Six of these patients were successfully weaned from ECMO; the mean duration of ECMO support was 9.1 days (range, 3.5–15.1 days). Indications for ECMO included pneumonia (8 cases required venovenous ECMO and 1 case required venoarterial [VA] ECMO), stress-induced cardiomyopathy due to fungemia (1 case required VA ECMO), and septic shock due to either urinary tract infection or unknown origin (2 cases required VA ECMO). In assessing risk factors leading to a failure of ECMO weaning, the pH on arterial blood gas analysis performed just before the beginning of this intervention was significantly lower in the nonsurvivors than in the survivors ($P = .046$).

Conclusions. ECMO can be a beneficial rescue therapy in immunosuppressed patients with cardiopulmonary dysfunction refractory to treatment. Severe acidosis before the administration of EMCO is a major determinant of ECMO weaning failure.

KIDNEY transplantation (kt) is a known therapeutic option for patients with end-stage renal disease. Immunosuppressive therapy is necessary for transplant recipients to prevent rejection of the graft, but these patients are consequently vulnerable to infections. Furthermore, infection and septic shock are the major causes of death of KT recipients, following cardiovascular disease.

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), in its actual application is an evolution of the heart–lung machines used in cardiac surgery; it is used to support respiratory function, circulation, or both. It has been proposed as a possible therapeutic option for patients with severe acute respiratory distress syndrome who have refractory hypoxia or hypercapnia [1]. Septic shock is no longer regarded as a contraindication to ECMO [2,3]. However, increased use of ECMO, with its associated need for resources, may also increase hospital costs [4]. It is therefore

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necessary to define risk factors for failure of ECMO weaning or death before starting ECMO support [5].

The purpose of the current study was to report the clinical outcomes of ECMO in KT recipients and to identify risk factors for ECMO weaning failure in these patients.

PATIENTS AND METHODS

We retrospectively reviewed the electronic medical records of KT patients who subsequently developed severe cardiopulmonary dysfunction refractory to conventional therapy and thus received ECMO in the surgical intensive care unit of the Asan Medical Center from December 2010 to December 2014. At baseline, age, sex, body mass index, underlying diseases, and characteristics of the KT cohort were recorded; this information included cause of end-stage renal disease, type of KT, AB0-incompatible KT, and previous rejection history. In addition, we recorded peri-ECMO variables, including cause of intervention, type of support provided, duration of ECMO and of mechanical ventilation before the procedure, and arterial blood gas analysis (ABGA) profiles measured just before the beginning of ECMO.

The indications for venovenous ECMO were persistent hypoxemia or hypercapnia refractory to conventional management. Indications for venoarterial (VA) ECMO support were coexistent cardiopulmonary injury, as well as profound shock despite vigorous resuscitation and administration of vasopressor agents. Patients were defined as survivors if they could be successfully weaned from ECMO and survive for at least 3 months thereafter.

Categorical variables are presented as frequencies and percentages; continuous variables are expressed as means with standard deviations or medians with ranges. All data were analyzed by using SPSS version 18 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, United States), and a P value $< .05$ was considered to be statistically significant.

RESULTS

Twelve patients who underwent KT and subsequently received ECMO during the 4-year period of this study were selected for analysis. The profiles of these cases are summarized in Table 1. In our study series, 6 patients were successfully weaned from ECMO and lived for at least 3 months after this treatment. The mean duration of ECMO support for these survivors was 9.1 days (range, 3.5–15.1 days). Conversely, the other 6 patients continued to receive ECMO support until death with no attempt made at weaning.

The study population comprised 8 male subjects and 5 female subjects. Seven KT procedures in our cohort involved living donors and 5 involved cadaveric donors. Among the 12 study patients, 5 patients were treated with steroids, rituximab, or bortezomib for graft rejection within 6 months of undergoing ECMO. All patients stopped immunosuppressive agents except low-dose steroids. The mean period between the KT and the ECMO support was 44.4 months (range, 1.2–184.3 months); 3 patients received ECMO support while staying in the hospital right after surgery, whereas the other 9 cases returned to the hospital through the emergency department.

Table 1. Patient Demographic and Clinical Characteristics of KT Patients Receiving ECMO

Case No.	Sex/Age	Cause of ESRD	KT Type	Previous Rejection	ECMO Start After KT (mo)	ECMO Type	ECMO Start After Symptom Onset (d)	Reason for ECMO	ECMO Duration (d)	Patient Survival[†]	
										3 Months	6 Months
1	M/57	DM	Living	Yes	178.2	VV	9	Viral pneumonia (influenza A)	15.1	Alive	Alive
2	M/53	DM	Cadaveric	Yes	9.5	VV	12	Combined viral/bacterial pneumonia (HMPV, *Streptococcus pneumoniae*)	8.7	Alive	Alive
3	M/62	HTN	Living	Yes	3.6[*]	VV	10	IPA with bacterial pneumonia (CRAB)	3.5	Alive	Alive
4	M/39	HTN	Living	No	184.3	VV	11	IPA with viral pneumonia (influenza A)	7.7	Alive	Alive
5	F/58	PCKD	Living	Yes	13.3	VA	2	Septic shock (r/o UTI)	7.9	Alive	Dead (4.8 mo)
6	M/34	CGN	Cadaveric	No	11.3	VV	21	Pneumocystis pneumonia	11.9	Alive	Dead (3.6 mo)
7	F/62	Unknown	Living	No	1.8[*]	VA	8	Septic shock (r/o pneumonia)	0.3	Dead	
8	F/54	DM	Living	Yes	1.0	VV	10	IPA with viral pneumonia (parainfluenza virus)	7.6	Dead	
9	M/32	Unknown	Cadaveric	No	111.3	VV	11	Viral pneumonia (rhinovirus)	12.8	Dead	
10	M/62	HTN	Cadaveric	No	1.9[*]	VV	35	IPA with bacterial pneumonia (CRPA)	2.5	Dead	
11	F/57	HTN	Cadaveric	No	1.2	VA	7	Fulminant myocarditis	23.2	Dead	
12	M/63	HTN	Living	No	15.0	VA	6	Bacterial pneumonia (*Klebsiella pneumoniae*)	2.6	Dead	

Abbreviations: CGN, chronic glomerular nephropathy; CRAB, carbapenem-resistant *Acinetobacter baumani*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; F, female; HMPV, human metapneumovirus; HTN, hypertension; IPA, invasive pulmonary aspergillosis; KT, kidney transplantation; M, male; PCKD, polycystic kidney disease; r/o, rule out; UTI, urinary tract infection; VA, venoarterial ECMO; VV, venovenous ECMO.

[*]ECMO started during the same hospital stay right after kidney transplantation.

[†]Survival time after weaning from ECMO. All nonsurvivor cases received the ECMO support until death.

During ECMO support, all patients concurrently underwent renal replacement therapy (RRT). Among the 6 patients in the survivor group, 5 received RRT for a mean period of 53 ± 37.5 days (range, 16–97 days) and were weaned from the RRT successfully, and the other patient continued with RRT. The indications for ECMO in our study population included pneumonia (8 cases required venovenous ECMO support and 1 case required VA ECMO support), fulminant myocarditis due to fungemia (1 case required VA ECMO support), and septic shock due to either urinary tract infection or unknown cause (2 cases required VA ECMO support). In the survivor group, 2 patients died at a later time after being successfully weaned from ECMO.

Table 2 presents a comparison of patient profiles between the survivor and nonsurvivor groups in our study series. There were no significant differences between the demographic features of the 2 groups. With regard to KT-related factors, the proportion of cadaveric to living donors was higher in the nonsurvivor group (50%) than in the survivor group (33.3%), and both of the ABO-incompatible KT recipients were nonsurvivors. However, these results were not statistically significant ($P = .455$). The duration of mechanical ventilation before the administration of ECMO was shorter in the survivor group than in the nonsurvivor group (3.7 ± 4.1 days vs. 6.0 ± 8.4 days; $P = .554$); moreover, the timing of ECMO after symptom onset was shorter among the survivors (10.8 ± 6.1 days vs. 12.8 ± 11.0 days; $P = .706$). However, these results were also not statistically significant. Among the pre-ECMO laboratory parameters, pH measurement on ABGA just before the administration of ECMO was the only factor found to be significantly associated with ECMO support failure ($P = .046$).

Table 2. Comparison of Patient Profiles Between the Survivor and the Nonsurvivor Groups

Variable	Survivors (n = 6)	Nonsurvivors (n = 6)	*P*
Demographic profiles			
Age, mean ± SD, y	50.5 ± 11.3	55.0 ± 11.8	.516
Male sex, no. (%)	5 (83.3)	3 (50.0)	.545
Diabetes mellitus, no. (%)	4 (66.6)	2 (33.3)	.567
HTN, no. (%)	6 (100.0)	5 (83.3)	.296
BMI, mean ± SD, kg/m^2	25.4 ± 4.0	23.9 ± 5.2	.588
KT-related factors, no. (%)			
Cadaveric donor	2 (33.3)	3 (50)	.753
ABO-incompatible	0	2 (33.3)	.455
Mechanical ventilation before ECMO, mean ± SD, d	3.7 ± 4.1	6.0 ± 8.4	.554
Laboratory profile just before the applying of ECMO, mean ± SD			
pH	7.33 ± 0.05	7.22 ± 0.11	.046
$PaCO_2$, mm Hg	32.7 ± 8.2	46.8 ± 19.0	.125
PaO_2, mm Hg	67.7 ± 18.6	81.2 ± 38.4	.456
Base excess, mEq/L	−7.58 ± 5.0	−8.68 ± 3.4	.663
Bicarbonate, mEq/L	17.5 ± 5.2	18.3 ± 3.8	.760
SaO_2, %	89.0 ± 9.2	85.8 ± 13.0	.637
Lactate, mmol/L	3.6 ± 3.7	3.3 ± 2.4	.850
PaO_2/FiO_2, mm Hg	67.7 ± 18.6	118.2 ± 125.0	.351
ECMO profile			
ECMO start after symptom, mean ± SD, d	10.8 ± 6.1	12.8 ± 11.0	.706
VA ECMO, no. (%)	1 (16.7)	3 (50)	.545
Duration of ECMO, mean ± SD, d	10.0 ± 3.6	9.3 ± 8.5	.863

Abbreviations: HTN, hypertension; BMI, body mass index; BSA, body surface area; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; KT, kidney transplantation; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SaO_2, arterial oxygen saturation; SD, standard deviation.

DISCUSSION

ECMO is the standard treatment for respiratory failure in newborn and pediatric patients who fail to respond to conventional treatment, and it is used to support respiratory function, circulation, or both. Septic shock is no longer regarded as a contraindication for ECMO. The overall survival of patients receiving adult respiratory ECLS is 55%, and overall cardiac ECLS survival is 44% in the general population [6].

In the current study, 50% of the KT patients were successfully weaned from ECMO, even though they were immunosuppressed. All of the included patients required supportive care because of severe sepsis. Although critical complications, such as acute cardiopulmonary dysfunction due to severe sepsis, do not frequently occur in KT recipients, these conditions are serious and life-threatening in these patients. Pneumonia was the major reason for providing ECMO support in the current patients. Five patients experienced severe rejection within 6 months of receiving ECMO support and were treated with steroids (all 5 patients), rituximab (3 of 5 patients), or bortezomib (1 of 5 patients). It is noteworthy that the risk of severe infection increases with increasing immunosuppression [7]. The outcomes in the current KT cohort suggest that ECMO can be a useful supportive therapy for immunosuppressed patients with severe sepsis.

The concurrent use of RRT during ECMO support reportedly improves fluid balance and caloric intake and reduces the use of diuretics, compared with ECMO alone [8]. In the current study, all of the KT patients concurrently underwent RRT while receiving ECMO support. After weaning from ECMO, only 1 patient in the survivor group has remained on RRT. This patient, who is currently still undergoing RRT, had received the graft organ 14.9 years before undergoing ECMO support, and the graft function in this individual was already decreased due to previous recurrent episodes of rejection and chronic allograft nephropathy.

In our assessment of the risk factors leading to failure of ECMO weaning, the pH level on ABGA measured before the administration of ECMO was significantly lower in the nonsurvivor group than in the survivor group. Other laboratory findings, including lactate levels, did not significantly differ between the 2 groups. The duration of mechanical

ventilation before the administration of ECMO and the timing of ECMO support after symptom onset were shorter in the survivor group than in the nonsurvivor group [9]. Although this result was not statistically significant, early intervention and more aggressive supportive care may improve outcomes in KT patients who require ECMO. Severe acidosis before the administration of EMCO is a predictor of failure to ECMO weaning.

CONCLUSIONS

There were some noteworthy limitations of this study. First, it involved retrospective analyses and second, it included only a small number of patients; thus, risk factor analysis could not be adequately performed. However, we can still conclude from our findings that ECMO may be a beneficial rescue therapy even in immunosuppressed patients such as KT recipients with a refractory pulmonary or cardiac condition.

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