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The effect of an improvement of experience and training in extracorporeal membrane oxygenation management on clinical outcomes

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Background/Aims: The use of extracorporeal membrane oxygenation (ECMO) is spreading rapidly, with successful procedures reported in the ECMO for Severe Adult Respiratory failure (CESAR) trial and treatment of the H1N1 pandemic. However, ECMO is associated with a high mortality rate. This study aimed to show that increased experience and improved teamwork through education may reduce the mortality rate associated with ECMO.
Methods: A retrospective study was performed. Data were collected from January 1, 2009, to December 31, 2011. The data were divided into two periods: 2009/2010 (period 1) and 2011 (period 2). The protocol and training program were applied during period 2.
Results: Seventy-six patients were included. The most common disease requiring ECMO support was pneumonia (43.4%). ECMO was applied within 7 days in 76.3% of patients. The primary outcomes, such as Intensive Care Unit (ICU) and hospital mortality rates, were higher during period 1 (91.3%) than period 2 (66.7%, p = 0.013). A multivariate analysis revealed that ECMO weaning failure was the only factor associated with ICU and hospital mortality (ICU mortality: hazard ratio [HR], 11.349; 95% confidence interval [CI], 1.281 to 100.505; p = 0.029; hospital mortality: HR, 17.976; 95% CI, 2.263 to 142.777; p = 0.006).
Conclusions: The mortality rate associated with the ECMO procedure decreased following the ECMO training program. However, applying the training program to ECMO management is not an independent factor for the mortality rate. Further studies should be performed to help reduce the mortality rate associated with ECMO.

Keywords: Extracorporeal membrane oxygenation; Respiratory insufficiency; Experience and education; Mortality

INTRODUCTION

The use of extracorporeal membrane oxygenation (ECMO)—a form of cardiopulmonary bypass—has recently become more widespread as a successful therapeutic option for patients who do not respond to conventional mechanical ventilator strategies. The popularity of ECMO as a treatment for acute respiratory failure has increased, especially since 2009 because of the H1N1 influenza pandemic and the ECMO for Severe Adult Respiratory

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failure (CESAR) trial [1]. Moreover, recently developed extracorporeal technologies have made ECMO less invasive and increased its use in patients with a diverse range of conditions. As a result, an Extracorporeal Life Support Organization (ELSO) Registry Report published in 2012 revealed 400 cases of adult respiratory failure ECMO cases during 2011. During 2013, the 223 international member centers of ELSO reported 4,357 cases [2].

However, ECMO is a high-risk procedure with a mortality rate of 25% [3]. Some of the many problems associated with ECMO include bleeding from the cannula or surgical sites, infection, oxygenator failure, tubing rupture, pump malfunction, intracranial hemorrhage, and seizures [2]. A few studies have shown that increased experience or familiarity with ECMO management is important for increasing the chances of patient survival and reducing the probability of mechanical component failures [3,4]. The National Institute for Health and Clinical Excellence guidelines have indicated that the relative inexperience of ECMO centers and the complications associated with ECMO contribute to the poor patient outcomes associated with the procedure [5].

The education provided through the ECMO training program is important for solving emergent, life-threatening problems and reducing the number of complications that can occur during the ECMO procedure [6,7]. Through protocol-based ECMO management, this training program is an effective way to improve knowledge, technical or behavioral skills, confidence levels, and teamwork among novice clinicians (physicians, residents, fellows of critical care medicine, cardiothoracic surgeons, perfusionists, Intensive Care Unit [ICU] nurses, and respiratory therapists).

The aim of this study was to show that improved experience gained through protocol-based ECMO management and a training program can reduce the mortality rate associated with ECMO.

METHODS

Study design and population

This retrospective study was approved by Institutional Review Board or Asan Medical Center, which waived informed consent (IRB No. 2011-0949). We enrolled patients 18 years of age or older who received ECMO support from January 1, 2009, to December 31, 2011, at the Asan Medical Center—a teaching hospital affiliated with the University of Ulsan and a tertiary care hospital in Seoul, South Korea. The study applied ECMO support according to the ELSO guidelines. ECMO support should be considered when the ratio of the partial pressure of oxygen in the blood to the fraction of inspired oxygen (PaO_2/FiO_2 [PF]) is lower than 150 mmHg, and ECMO is indicated when the ratio is lower than 80 mmHg. Moreover, an arterial carbon dioxide tension higher than 80 mmHg or an end-inspiratory plateau pressure (PIP) higher than 30 cm H_2O indicates the use of ECMO in patients with adult respiratory distress syndrome (ARDS) [8]. The data were divided into two periods of ECMO support: 2009/2010 (period 1) and 2011 (period 2). The protocol-based ECMO management and training program were applied during period 2.

Definitions and variables

We collected the following patient demographic data retrospectively: age, sex, type of ECMO and oxygenator, elapsed time between ventilator use and ECMO application, frequency of oxygenator change, presence or absence of ECMO weaning, complications, and death. ECMO was divided into two types: veno-venous (V-V) and veno-arterial (V-A). The primary outcomes were defined as hospital mortality, ICU mortality, and 28-day mortality.

Protocol-based ECMO management

The ECMO protocol was based on ELSO guidelines from cannulation to decannulation after weaning from the procedure. Depending on the ECMO protocol, clinicians conducted ECMO set-up and checked the parameters for monitoring. Coagulation status was monitored by activated partial thromboplastin time rather than the more commonly used activated clotting time. If patients displayed a tendency towards bleeding or disseminated intravascular coagulation, nafamostat mesilate (Futhan, SK Life Science, Seoul, Korea) was used instead of unfractionated heparin. According to the ELSO guidelines, lung-protective ventilation was applied for lung rest. The positive end-expiratory pressure (PEEP) was usually set to avoid atelectasis caused by a small tidal volume [8].

Weaning occurred after the underlying disease was

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successfully treated and lung function improved (fraction of inspired oxygen lower than 0.5, PEEP lower than 10 cm H_2O, PIP lower than 27 cm H_2O) [9]. For V-V ECMO, the ventilator setting was adjusted before both the sweep gas supply and oxygenator were stopped. For V-A ECMO, the blood flow was reduced slowly before the inotropics dose and ventilator settings were adjusted to acceptable levels. The ECMO circuit was then clamped off before perfusion, gas exchange, and decannulation were performed. Furthermore, an ECMO technique checklist was used to reduce the preparation time of ICU nurses and the time needed to replace the ECMO tube.

Education and team development

The ECMO team comprised a critical care medicine specialist, cardiothoracic surgeons, perfusionists, ICU nurses, and a respiratory therapist. ECMO training was provided every month by the Asan Medical Center ECMO program staff. The curriculum consisted of didactic lectures, hands-on simulations for set-up and priming, and problem-solving skills for emergency ECMO scenarios. The content of the lectures included basic hemodynamics, ECMO physiology, circuit anatomy, and hemostasis of patients on ECMO. Extracorporeal life support (ECLS) circuit troubleshooting, as well as discussions about the in-hospital ECMO protocol and the importance of team communication were also included in the training lectures. The ECMO equipment used for simulation consisted of a standard Maquet PLS System (Quadrox, Maquet Inc., Wayne, NJ, USA), including a Rotaflow centrifugal pump and a polymethylpentene (PMP) oxygenator (Maquet Inc.).

Statistical analysis

We used the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) to statistically analyze the data. Continuous variables are expressed as median (range), unless otherwise indicated. Categorical variables are expressed as numbers (%). Differences among the continuous groups were compared using Student *t* test or the Mann-Whitney *U* test. Differences among the categorized groups were compared using the chi-square test or Fisher exact test. In statistical testing, two-sided $p < 0.05$ was considered to denote statistical significance. Logistic regression analysis determined the odds ratio (OR) between two periods of ECMO support. Finally, the Cox proportional hazard model was used to determine which risk factors led to death.

RESULTS

ECMO support was given to 84 patients from January 1, 2009, to December 31, 2011, at Asan Medical Center. Because eight of these patients received ECMO support as part of a procedure, the study cohort included only 76 patients. The median age of the patients receiving ECMO support was 55 years, and 57.9% (44/76) were male. The most common diseases that required ECMO support were pneumonia (43.4%), sepsis (17.1%), ARDS (13.2%), and respiratory failure (10.5%). All patients received mechanical ventilation during ECMO support, with ECMO applied within seven days in 76.3% (58/76) of patients. The initial type of ECMO used was V-V in 46 patients (60.5%) and V-A in 30 patients (39.5%). The most common type of oxygenator used was CAPIOX (90.8%, Terumo, Tokyo, Japan); Quadrox (2.6%) was the next most commonly used type. The median number of oxygenator membrane changes was two times (range, 0 to 10) (Table 1). The median PF ratio that necessitated ECMO support was 66 mmHg, and the anticoagulant used was heparin only (65.8%), nafamostat mesilate only (2.6%), or a switch from heparin to nafamostate mesilate (31.6%). Of the 76 patients evaluated in the present study, 29 (38.2%) had been weaned from ECMO, and the duration of ECMO for patients who were weaned was 6.5 days. The 28-day mortality was 64.5%, and ICU or hospital mortality rates were equal at 81.6%. The causes of death were pneumonia (46.9%) and aggravated underlying diseases (28%). The median duration of the ICU stay was 19 days (Table 2).

There were no significant differences in baseline characteristics between the two periods of ECMO support. Nonetheless, more patients had ARDS during period 2 than period 1 (26.7% vs. 4.3%, $p = 0.011$) (Table 3). The primary outcomes, such as ICU and hospital mortality, between the two periods were equally significant (91.3% in period 1 vs. 66.7% in period 2, $p = 0.013$). Nonetheless, there was no significant difference in the 28-day mortality rate between the two periods (71.7% in period 1 vs. 53.3% in period 2, $p = 0.101$) (Table 4). The

Table 1. Baseline characteristics of the study patients who received ECMO support (n = 76)

Characteristic	Value
Age, yr	55 (16–89)
Male sex	44 (57.9)
CVVHD application	33 (43.4)
Diseases requiring ECMO support	
Pneumonia	33 (43.4)
Sepsis	13 (17.1)
Cardiologic problems	7 (9.2)
Adult respiratory distress syndrome	10 (13.2)
Respiratory failure	8 (10.5)
Upper airway obstruction	5 (6.6)
The days from ventilator to ECMO	2 (1–40)
From ventilator to ECMO support, day	
< 7	58 (76.3)
≥ 7	18 (23.7)
Types of ECMO	
Veno-venous	46 (60.5)
Veno-arterial	30 (39.5)
Types of oxygenator	
CAPIOX (Termo)	69 (90.8)
Quadrox (Maquet)	2 (2.6)
Phisio (Sorin)	5 (6.6)
Frequency of oxygenator membrane change	
No change	39 (51.3)
1 Change	16 (21.1)
2 Changes	6 (7.9)
3 Changes	6 (7.9)
4 Changes	5 (6.6)
≥ 5 Changes	4 (5.2)

Values are presented as median (range) or number (%).
ECMO, extracorporeal membrane oxygenator; CVVHD, continuous veno-venous hemodialysis.

mortality rate was higher during period 1 than period 2 (OR, 5.250; 95% confidence interval [CI], 1.466 to 18.806 for ICU and hospital mortality, respectively; p = 0.011). A multivariate analysis revealed that ECMO weaning failure was the only factor significantly associated with ICU and hospital mortality (for ICU mortality: hazard ratio [HR], 11.349; 95% CI, 1.281 to 100.505; p = 0.029; for hospital mortality: HR, 17.976; 95% CI, 2.263 to 142.777; p = 0.006) (Table 5).

Table 2. Outcomes in patients with ECMO support (n = 76)

Characteristic	Value
ECMO weaning	29 (38.2)
ECMO support time, day	6.5 (0.1–15.3)
Complications	
Bleeding	19/26 (73)
Peripheral ischemia	2/26 (7.7)
Arrhythmia	2/26 (7.7)
Catheter problem	1/26 (3.8)
ECMO clot	1/26 (3.8)
Others	1/26 (3.8)
ICU mortality	62 (81.6)
Hospital mortality	62 (81.6)
28-Day mortality	49 (64.5)
ICU length of stay, day	19 (1–124)
Hospital length of stay, day	28 (2–225)
Causes of death	
Pneumonia	30/64 (46.9)
Bleeding	4/64 (6.3)
Respiratory failure	3/64 (4.7)
Septic shock	5/64 (7.8)
Underlying disease aggravation	18/64 (28)
Others	4/64 (6.3)

Values are presented as number (%) or median (range).
ECMO, extracorporeal membrane oxygenator; ICU, Intensive Care Unit.

DISCUSSION

The current study has shown that experience and training are essential to the success of a new ECMO center. With the successful use in the CESAR trial and H1N1 influenza pandemic and improvements in technologies such as pumps and membranes, ECMO use is spreading very rapidly worldwide. However, ECMO is a high-risk procedure, so education about and experience with this method are both very important. Recent reports have demonstrated the important role that ECMO plays in the treatment of ARDS, showing an improved survival rate of 55% to 65% in patients undergoing ECMO. Moreover, the ELSO registry reported in 2012 showed as many as 400 ECMO cases among ARDS patients each year after the H1N1 pandemic. In 2013, ELSO had 223 international member centers, and reported data for 4,357 cases to the registry [2]. As a consequence, many new centers

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Table 3. Baseline characteristics for period 1 and period 2 of ECMO support

Characteristic	Period 1 (n = 46)	Period 2 (n = 30)	*p* value
Age, yr	58 (18–89)	50 (16–78)	0.445
Male sex	31 (67.4)	13 (43.3)	0.038
CVVHD application	23 (50)	10 (33.3)	0.194
Diseases requiring ECMO support			
Pneumonia	22 (47.8)	11 (36.7)	0.337
Sepsis	11 (23.9)	2 (6.7)	0.051
Cardiologic causes	5 (10.9)	2 (6.7)	0.697
Adult respiratory distress syndrome	2 (4.3)	8 (26.7)	0.011
Respiratory failure	3 (6.5)	5 (16.7)	0.252
Upper airway obstruction	3 (6.5)	2 (6.7)	1.000
The days from ventilator to ECMO	2 (1–36)	2.5 (1–40)	0.331
From ventilator to ECMO support, day			0.954
< 7	35 (76.1)	23 (76.7)	
≥ 7	11 (23.9)	7 (23.3)	
Types of ECMO			0.686
Veno-venous	27 (58.7)	19 (63.3)	
Veno-arterial	19 (41.3)	11 (36.7)	
Types of oxygenator			0.142
CAPIOX (Termo)	42 (91.3)	27 (90)	
Quadrox (Maquet)	0	2 (6.7)	
Phisio (Sorin)	4 (8.7)	1 (3.3)	

Values are presented as median (range) or number (%).
ECMO, extracorporeal membrane oxygenator; CVVHD, continuous veno-venous hemodialysis.

are starting to adopt the ECMO procedure.

In the present study, the mortality rate was markedly lower during period 2 than period 1. This may be a result of the experience accumulated by staff over many years in using ECMO, and the protocol-based ECMO training and education that was introduced during period 2. Many studies have reported volume-outcome relationships [10-12]. A recent study reported that clinician experience or specific processes of high-volume centers might be associated with the clinical outcomes of severely ill patients suffering from acute respiratory failure. This volume-outcome relationship might stem from the beneficial effects of more experienced practitioners or from referrals to centers that have systematic processes that produce better outcomes [13]. In addition, a recent report that analyzed the ELSO registry has described improved outcomes in mechanical component failure associated with ECMO between two different periods (15.8% in 1987 to 1996 vs. 13.8% in 1997 to 2006, $p < 0.001$) [4]. The differences were attributed to the accumulation of experience.

Clinicians trained at high-volume hospitals might have more experience in recognizing and managing critical illness, which may reduce the incidence of morbidity and mortality caused by ECMO [11,14]. Furthermore, concomitant multidisciplinary care is associated with reduced time spent in the ICU and the overall hospital length of stay [15], as is the presence of a trained intensivist [16]. In the present study, an intensivist supervised the ECMO set-up, expert cannulation, management of the circuitry, and adherence to ECMO protocols to prevent human error. However, new and small-volume ECMO centers might not be able to offer this level of support, which would increase the risks associated with ECMO.

We implemented a protocol-based ECMO training

Table 4. Comparison of outcomes during period 1 and period 2 of ECMO support

Characteristic	Period 1 (n = 46)	Period 2 (n = 30)	*p* value
ECMO weaning,	17 (37)	12 (40)	0.789
ECMO support time, day	6.7 (0.1–10.7)	5.4 (1.5–15.3)	0.467
Complications			0.298
Bleeding	13/18 (72.2)	6/8 (75)	
Peripheral ischemia	2/18 (11.1)	0/8 (0)	
Arrhythmia	2/18 (11.1)	0/8 (0)	
Catheter problem	0/18 (0)	1/8 (12.5)	
ECMO clot	1/18 (5.6)	0/8 (0)	
Others	0/18 (0)	1/8 (12.5)	
ICU mortality	42 (91.3)	20 (66.7)	0.013
Hospital mortality	42 (91.3)	20 (66.7)	0.013
28-Day mortality	33 (71.7)	16 (53.3)	0.101
ICU length of stay, day	18 (1–99)	23.5 (3–124)	0.159
Hospital length of stay, day	26 (2–81)	36 (4–225)	0.611
Causes of death			0.017
Pneumonia	24/42 (57.1)	6/20 (30)	0.068
Bleeding	3/42 (7.1)	1/20 (5)	1.000
Respiratory failure	2/42 (4.8)	1/20 (5)	1.000
Septic shock	1/42 (2.4)	3/20 (15)	0.087
Underlying disease aggravation	11/42 (26.2)	7/20 (35)	0.410
Others	1/42 (2.4)	2/20 (10)	0.583

Values are presented as number (%) or median (range).
ECMO, extracorporeal membrane oxygenator; ICU, Intensive Care Unit.

Table 5. Multivariate analysis for ICU and hospital mortality

Variable	ICU mortality			Hospital mortality		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
ECMO weaning failure	11.349	1.281–100.505	0.029	17.976	2.263–142.777	0.006
Period 1	3.660	0.440–30.465	0.230	3.437	0.551–21.432	0.186
ICU LOS	0.898	0.741–1.088	0.271	0.848	0.694–1.036	0.107
Hospital LOS	0.992	0.945–1.042	0.757	1.006	0.960–1.055	0.793

ICU, Intensive Care Unit; CI, confidence interval; ECMO, extracorporeal membrane oxygenator; LOS, length of stay.

program to educate both novice residents on monthly rotations, as well as new ICU nurses. Following didactic lectures, hands-on simulations provided novices with the opportunity to practice the technical and behavioral skills necessary to manage emergency ECMO scenarios. After the ECMO training program, the subjects had the confidence to manage life-threatening ECMO-related problems in a timely manner and demonstrated improved technical and behavioral skills. Furthermore, assistance by trained ICU nursing staff reduced the time needed to prepare materials and improved the nursing approach used for ECMO management. Two recent reports have shown that a simulation-based ECMO training program is effective in solving life-threatening problems that can occur during ECMO application, and can improve technical or behavioral skills, safety knowledge, and teamwork for ECMO management [6,7].

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The techniques used for ECMO therapy have undergone substantial changes over the past decade. With the introduction of a new generation of PMP membrane oxygenators and a centrifugal pump, which are key elements of the ECMO system, there have been reductions in mechanical failures (such as flow dynamics), and in the levels of both hemolysis and heat generation [17]. All of these effects allowed for long-lasting use of ECMO.

In the case of respiratory ECLS, the ELSO registry published in 2012 reported a 16.1% oxygenator failure rate and a 2.1% pump malfunction rate in patients older than 16 years of age [2]. Nevertheless, the ECMO mortality rate ranged from 21% to 41% [1,18,19]. While 73.3% of perfusion accidents were attributed to human error, 19.5% were attributed to device malfunctions or failures [20].

The lung-protective ventilation with ECMO application that was implemented in the current study is considered to contribute to improved survival. A recent study introduced the concept of "medical ECMO," which shifts the treatment of ARDS from device management to disease management [21]. The use of ECMO enables the lung to rest in patients with ARDS or respiratory failure by minimizing ventilator-induced lung injury [1,22-24]. By providing sufficient oxygen at a low inflation pressure, lung-protective ventilation reduces ventilator-induced lung injury and ventilator-associated oxygen toxicity by permissive hypercapnia or limited use of inspired oxygen [9,25,26]. Lung-protective ventilation with ECMO might enhance lung protection with a tidal volume lower than 6 mL/kg, and the respiratory acidosis that results can be efficiently managed by ECMO [27].

The present study has some limitations. First, it was a retrospective study performed at a single institution. Our data were extracted from an in-house electronic system of medical records. It might not be appropriate to extrapolate the results of our study to other centers that offer different treatment strategies and structures. Second, we focused on the aspect of ECMO management that relates specifically to the time spent in the ICU. Most of our patients who received ECMO had life-threatening conditions at the time of ICU admission. Patient outcomes are determined by whether appropriate and timely management are received at the ward or emergency department as well as after ICU admission. These factors were not investigated in the present study. Third, in the present study, there was a difference in the baseline characteristics of patients. Patients with ARDS during period 2 were more contained than during period 1 (26.7% vs. 4.3%, $p = 0.011$) and patients with pneumonia or sepsis during period 1 were more contained than during period 2 (pneumonia: 47.8% vs. 36.7%, $p = 0.337$; sepsis: 23.9% vs. 6.7%, $p = 0.051$). It is possible that mortality is associated with differences in these baseline characteristics. However, five patients with ARDS during period 2 had humidifier disinfectant-associated interstitial lung disease, which emerged in South Korea in 2011. These patients received ECMO due to ARDS and had higher disease severity and mortality rates than patients with pneumonia or sepsis. Most of these patients had progressed to the fibrotic phase of ARDS and their ECMO weaning had failed, leading to death while on a waiting list for lung transplantation. Therefore, the mortality rate difference between period 1 and period 2 may be explained by an accumulation of experience and knowledge by hospital staff through education and training for ECMO rather than a difference in baseline characteristics. However, applying a training program for ECMO management is not an independent factor for mortality.

In conclusion, mortality is decreased in patients with ECMO after ECMO program. However, applying the training program for ECMO management is not an independent factor for mortality, and further study is needed to reduce the mortality caused by ECMO.

KEY MESSAGE

1. Extracorporeal membrane oxygenation (ECMO) is a high-risk procedure and plays in the treatment of severely ill patient, showing an improved survival rate.
2. Protocol-based ECMO education and experience which are not an independent factor decreased mortality rate.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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