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Original Article / Özgün Makale

Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: our single-center experience

Akut solunum sıkıntısı sendromunda venovenöz ekstrakorporeal membran oksijenasyonu: Tek merkezli çalışma deneyimimiz

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ABSTRACT

Background: In this study, we present our five-year experience with venovenous extracorporeal membrane oxygenation for the treatment of acute respiratory distress syndrome.

Methods: Between November 2010 and November 2015, 33 patients (24 males, 9 females; mean age: 48.6±14.7 years; range 19 to 76 years) with acute respiratory distress syndrome refractory to conventional therapy were supported with venovenous extracorporeal membrane oxygenation. The general indication for venovenous extracorporeal membrane oxygenation support was refractory hypoxia, hypercapnia, and respiratory acidosis, despite the optimization of conventional therapy. Detailed clinical data of the patients were retrospectively analyzed.

Results: Cannulation was achieved via femoral-femoral veins in 24 patients (73%) and jugular-femoral veins in nine patients (27%). The median duration of venovenous extracorporeal membrane oxygenation support was 17 (range, 1 to 52) days. The most common complication was minor bleeding in six patients (18%). Eighteen patients (54.5%) were successfully weaned from venovenous extracorporeal membrane oxygenation support. Of these patients, 13 (39.4%) survived and were discharged from the hospital.

Conclusion: Venovenous extracorporeal membrane oxygenation can be a life-saving treatment modality in patients with severe acute respiratory distress syndrome. Improved results may be provided with increased experience and an established standard protocol for the management of venovenous extracorporeal membrane oxygenation.

Keywords: Acute respiratory distress syndrome; life-saving modality; venovenous extracorporeal membrane oxygenation.

ÖZ

Amaç: Bu çalışmada, akut solunum sıkıntısı sendromunun tedavisinde venovenöz ekstrakorporeal membran oksijenasyonuna ilişkin beş yıllık deneyimimiz sunuldu.

Çalışma planı: Kasım 2010 - Kasım 2015 tarihleri arasında konvansiyonel tedaviye dirençli akut solunum sıkıntısı sendromlu 33 hastaya (24 erkek, 9 kadın; ort. yaş 48.6±14.7 yıl; dağılım 19-76 yıl) venovenöz ekstrakorporeal membran oksijenasyonu desteği uygulandı. Venovenöz ekstrakorporeal membran oksijenasyonu desteğinin genel endikasyonu, konvansiyonel tedavinin optimizasyonuna rağmen, refrakter hipoksi, hiperkapni ve solunumsal asidoz idi. Hastaların detaylı klinik verileri retrospektif olarak incelendi.

Bulgular: Kanülasyon 24 hastada (%73) femoral-femoral venlerden, dokuz hastada (%27) juguler-femoral venlerden gerçekleştirildi. Ortalama venovenöz ekstrakorporeal membran oksijenasyon desteği 17 (dağılım, 1-52) gün idi. En sık görülen komplikasyon, altı hastada (%18) minör kanama idi. On sekiz hasta (%54.5) başarılı bir şekilde venovenöz ekstrakorporeal membran oksijenasyonu desteğinden ayrıldı. Bu hastaların 13'ü (%39.4) sağkaldı ve hastaneden taburcu edildi.

Sonuç: Venovenöz ekstrakorporeal membran oksijenasyonu, şiddetli akut solunum sıkıntısı sendromlu hastalarda hayat kurtarıcı bir tedavi yöntemi olabilir. Sonuçların iyileşmesi, deneyimlerin artması ve venovenöz ekstrakorporeal membran oksijenasyonunun tedavisine yönelik standart bir protokolün oluşturulması ile sağlanabilir.

Anahtar sözcükler: Akut solunum sıkıntısı sendromu; hayat kurtarıcı modalite; venovenöz ekstrakorporeal membran oksijenasyonu.

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Acute respiratory distress syndrome (ARDS) is characterized by new-onset hypoxemia and bilateral pulmonary infiltrates which are consistent with pulmonary edema without any evidence of cardiac insufficiency.[1] Underlying diseases are of pulmonary origin, including bilateral pneumonia and aspiration, or secondarily affecting the lung, such as sepsis, trauma, and massive transfusion.[2] Despite the advancements in the intensive care during the past decades, the mortality and morbidity of patients with ARDS still remain high.[3-5] The Berlin definition of ARDS classifies the severity of the disease as mild, moderate, and severe with mortality rates of 20%, 41%, and 52%, respectively.[6]

Extracorporeal membrane oxygenation (ECMO) is recommended as an advanced treatment modality for severe ARDS, if other rescue strategies fail. Previous studies have shown the benefit of venovenous ECMO (vv-ECMO) support for this indication.[7,8] In 2009, the conventional ventilatory support versus ECMO for severe adult respiratory failure (CESAR) study has demonstrated an important survival benefit with use of ECMO for patients with severe ARDS.[9]

To the best of our knowledge, no study has yet performed to investigate the effectiveness of vv-ECMO support for patients with ARDS in Turkey. In this study, therefore, we present our five-year experience with vv-ECMO for the treatment of patients with ARDS.

PATIENTS AND METHODS

The study protocol was approved by the Medical Research Ethics Committee of our institution. The study was conducted in accordance with the principles of the Declaration of Helsinki. Between November 2010 and November 2015, vv-ECMO was initiated in 33 patients (24 males, 9 females; mean age: 48.6±14.7 years; range 19 to 76 years) with ARDS refractory to all conventional therapeutic modalities. The causes of ARDS were primary lung failure in 24 patients (72.7%), including bacterial, viral, H1N1, fungal and aspiration pneumonia, or secondary lung failure due to sepsis in three patients (9.1%), trauma in three patients (9.1%), and postoperative pulmonary complication in three patients (9.1%). The general indication for vv-ECMO was refractory hypoxia, hypercapnia, and respiratory acidosis, despite the optimum treatment with mechanical ventilation. Detailed clinical data of the patients were retrospectively analyzed.

The ECMO system, setup, and cannulation

The ECMO was connected to the circulation of the patients to an external blood pump and artificial lung for temporary life support. The ECMO circuit was consisted of a centrifugal pump, membrane oxygenator, inlet and outlet cannulas, and circuit tubing. The exchange of oxygen and CO_2 was taken place in the oxygenator, which delivered the re-oxygenated blood back into the vein. Additional ports may be added for hemodialysis or ultrafiltration. The ECMO circuit did not include a venous reservoir, venous bubble trap, or arterial filter.

The ECMO support was set in the intensive care unit (ICU) in all patients. The prime solution prepared in 1000 mL of physiological saline solution by adding 1000 IU unfractionated heparin. Due to its possible effect to create a breeding ground for microorganisms on the wound surface draped for more than a day, povidone iodine was not preferred and, instead, chlorhexidine was used for skin preparation.[10]

All cannulations were carried out at the bedside by cardiovascular surgeons using the Seldinger's percutaneous technique except for one case. The guidewire was inserted after the vessel puncture and, then, the cannulas (Maquet HLS cannula; BIOLINE coating, Germany) were inserted through the guidewire into the vessels. A 40 to 45 cm long cannula was advanced via the femoral vein to the inferior caval vein for drainage. Venous return was achieved via a contralateral femoral vein or right internal jugular vein. The size of the cannulas was selected according to the body weight of the patient. The sizes of the cannulas were 17 to 25 French (Fr) for inflow and 21 to 28 Fr for outflow. The cannulas were connected to the ECMO machine (Maquet, Rotaflow: BE-PLS 12050-Quadrox PLS [Jostra], Germany) by tubing. The pump flow of ECMO was adjusted according to the body surface area of 2-2.5 L/m^2. All cannulas were sutured to the skin. Location of the cannula was confirmed by fluoroscopy. After the ECMO setup was completed, the final view is shown in Figure 1.

Anticoagulation

The anticoagulation protocol was based on intravenous unfractionated heparin application. Unfractionated heparin infusion was intravenously initiated before the cannulation and administered continuously to keep an activated clotting time (ACT) of 150 to 200 seconds. An optimum ACT level was approximately 165 to 170 seconds. It was measured every four hours, and unfractionated heparin infusion dose was adjusted according to the ACT.

Follow-up during ECMO

The ECMO specialists and nurses ensured exclusive regular monitoring of coagulation, perfusion and

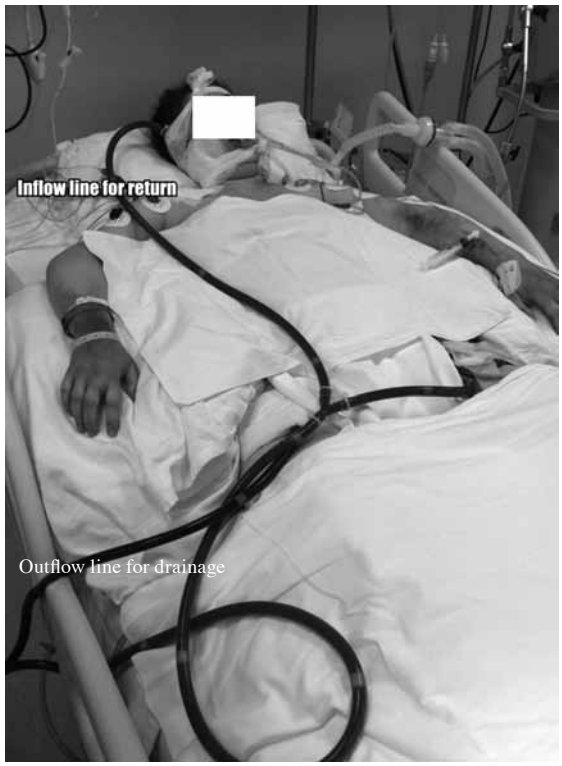

Figure 1. Final view after extracorporeal membrane oxygenation setup is completed.

neurological status, and circuit conditions for each patient who received ECMO support. The specialists and nurses paid a particular attention to the following issues: existence of a clot in the oxygenator membrane, any color difference between the drainage and return catheters and increased oxygenator/membrane pressure gradient. Post-oxygenator partial oxygen pressure and hemoglobin level were checked daily. The ECMO system replacement was carried out in case of disruption of gas exchange function of oxygenator, declined ECMO blood flow, or any evidence of hemolysis.

Following the initiation of the ECMO support, the ventilator setting was often adjusted to allow 'lung rest' (FiO_2: 0.4, positive end-expiratory pressure: 10 cmH_2O, tidal volume: 4 mL/kg, rate: 12/min, inspiratory/expiratory ratio: 1/1.5) by ICU specialists.

Benzodiazepines and narcotics were used for sedation. Propofol was not preferred due to its potential interaction with oxygenator membrane. Antibiotherapy was routinely initiated and modified according to proven microbial infections using the results of antibiogram. Enteral nutrition was initiated as early as possible according to our ICU nutrition protocol. Fluid balance was kept with diuretics and continuous venovenous hemofiltration, if clinically indicated. Continuous venovenous hemofiltration was used in case of acute kidney injury, excessive fluid gain, and metabolic acidosis.

Combined positioning therapy was a routine practice in the treatment of patients with ARDS which comprised 135 degrees prone positioning and continuous lateral rotational therapy, and was applied by the ICU specialists and nurses.

Decannulation

Unfractionated heparin infusion was discontinued 60 minutes before decannulation. Decannulation was carried out at the bedside in each patient. Both return and drainage cannulas were removed simultaneously. Then, direct manual compression was carried out to the decannulation areas for at least 30 minutes.

Statistical analysis

Statistical analysis was performed using PASW version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean ± standard deviation. Categorical variables were expressed in frequency and percentages. All pre-ECMO demographic, clinical, and laboratory variables were analyzed by univariate logistic regression analysis to identify the independent predictors of the mortality. Two tailed p values of <0.05 were considered statistically significant with a confidence interval (CI) of 95%.

RESULTS

Baseline characteristics of the patients are shown in Table 1.

Ten patients underwent surgery before ECMO support which was lung resection in six, open heart surgery in one, neurosurgical intervention in one, orthopedic intervention in one, and caesarean section in one patient. The most common cause for ECMO support was pneumonia in 72.7% of the patients. The median duration of ICU stay and mechanical ventilatory support before the initiation of ECMO were 13.0 days (range, 0 to 45 days) and 6.7 days (range, 0 to 37 days), respectively.

Cannulation was achieved via femoral-femoral veins in 24 patients (73%) and jugular-femoral veins in nine patients (27%). All venous accesses, except the one which was performed by the cut-down technique, were achieved percutaneously. The predominant sizes of the outflow and inflow cannulas were 23 Fr and 21 Fr, respectively. The median duration of vv-ECMO support was 17 days (range, 1 to 52 days).

Table 1. Baseline characteristics of patients treated with extracorporeal membrane oxygenation

Characteristics	All patients			Survivors			Non-survivors			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Number of patients	33			13			20			
Age (years)			48.6±14.7			44.4±11.6			51.4±16.1	0.128
Gender										0.491
Male	24			10			14			
Female	9			3			6			
Body weight (kg)			78.1±12.9			79.2±10.1			77.5±14.8	0.434
Height (cm)			171.1±7.9			170.0±7.8			171.9±8.0	0.928
Body surface area (m^2)			1.9±0.2			1.9±0.2			1.9±0.2	0.957
Underlying diseases										
Chronic lung disease	8	24.2		3	23.1		5	25.0		0.619
Hypertension	8	24.2		3	23.1		5	25.0		0.619
Malignancy	6	18.2		1	7.7		5	25.0		0.217
Diabetes mellitus	4	12.1		2	15.4		2	10.0		0.519
Chronic renal failure	2	6.1		2	15.4		0	0		0.148
Liver cirrhosis	2	6.1		1	7.7		1	5.0		0.640
The cause of ARDS										
Pneumonia	24	72.7		9	69.2		15	75.0		0.509
ARDS secondary to sepsis	3	9.1		2	15.4		1	5.0		0.338
Trauma	3	9.1		1	7.7		2	10.0		0.662
Postoperative ARDS	3	9.1		1	7.7		2	10.0		0.662
Laboratory test before ECMO										
pH			7.2±0.1			7.15±0.1			7.13±0.1	0.703
$PaCO_2$ (mmHg)			79.5±11.8			78.1±10.4			80.4±12.9	0.730
PaO_2 (mmHg)			68.4±8.0			70.2±6.2			67.3±8.9	0.281
SaO_2			74.7±8.3			79.3±5.4			71.8±8.6	0.180
Lactic acid (mmol/L)			58.1±19.4			57.0±21.1			58.9±18.7	0.524

SD: Standard deviation; ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; $PaCO_2$: Partial pressures of carbon dioxide; PaO_2: Partial pressures of oxygen; SaO_2: Oxygen saturation.

The most common complication was minor bleeding in six patients (18%) and was controlled by manual compression without requiring any surgical revision. Other complications were deep vein thrombosis (DVT) in three, oxygenator head thrombosis in one, and vascular injury of THE right femoral vein in one patient which caused major bleeding and required surgical repair. The mean amount for blood products during the ECMO support was 5±8 units of packed red blood cells, 6±16 units of fresh frozen plasma, and 2±3 units of platelet suspensions. Four patients (12%) did not require transfusion. The outcomes of ECMO are shown in Table 2.

In addition, 18 patients (54.5%) were successfully weaned from the ECMO support. Of these patients, 13 (39.4%) survived and were discharged from the hospital. The in-hospital mortality rate was 60.6%, and the most common cause was multi-organ failure leading to cardiovascular collapse in 12 patients (60%). The other causes of mortality were worsening of ARDS, despite extensive ECMO support (25%), heart failure (5%), intracranial hemorrhage (5%), and major bleeding (5%).

The univariate analysis of baseline characteristics of patients and other variables following the initiation of ECMO revealed no significant predictor of the mortality.

Table 2. Outcomes of extracorporeal membrane oxygenation

	All patients (n=33)	Survivors (n=13)	Non-survivors (n=20)	
	Mean±SD	Mean±SD	Mean±SD	*p*
ECMO duration (days)	17.0±14.0	14.4±12.5	18.7±15.0	0.501
Ventilator duration (days)	24.5±17.5	25.8±19.1	23.7±16.8	0.870
ICU LOS (days)	26.9±18.2	30.5±20.4	24.5±16.7	0.598
Hospital LOS (days)	29.5±20.2	35.2±23.6	25.8±17.2	0.353

ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; LOS: Length of stay.

DISCUSSION

The ECMO therapy was first described successfully in a patient with post-traumatic respiratory failure in 1972.[11] However, after this case report, two randomized-controlled clinical studies, which were accepted as valuable trials, failed to demonstrate any significant benefit of the ECMO support.[12,13] The use of ECMO therapy in adults, thus, remained limited, until the publication of the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial in 2009, which demonstrated a significant benefit of ECMO therapy in terms of survival for patients with severe respiratory failure and ARDS caused by H1N1 pandemic.[9] The CESAR trial is a randomized-controlled, multi-center clinical study and included a total of 180 patients with severe respiratory failure. These patients were randomly divided into two groups: conventional management and ECMO groups. The primary outcome of the trial was mortality or severe disability at six months after randomization or before discharge, which was observed in 37% of the patients in ECMO group, compared to 53% patients in the conventional management group. Based on the results of this study, the authors concluded that ECMO therapy could significantly improve survival without severe disability in patients with severe, but potentially reversible respiratory failure.

The Extracorporeal Life Support Organization (ELSO) Registry report was published in July 2012.[14] In this report, 3,280 adults were supported for respiratory failure, and 1,808 of them survived to discharge or referral. The overall survival rate was 55%. In a study of Hemmila et al.,[15] the authors reported their large-case series (n=255) and 14-year experience with ECMO for the treatment of ARDS. In their study, the weaning rate from ECMO was found to be 67%, overall survival to discharge rate to be 52%, and survival to discharge rate for vv-ECMO support to be 59.5%. In addition, Schmid et al.[16] reported their case series consisting of 176 adult patients with acute lung failure treated with vv-ECMO. The overall survival rate was 56% in their series. In another cases series including 85 ARDS patients treated with ECMO reported by Roch et al.,[17] and the survival rate was found to be 44%. In our study, the success rate of ECMO weaning was 54.5% (18/33) and overall survival to discharge rate was 39.4% (13/33), consistent with the previous findings.

Both venovenous and venoarterial ECMO can be used with other therapeutic approaches for the treatment of ARDS. A recent study have shown that vv-ECMO is as reliable as venoarterial ECMO in patients without any evidence of organ failure, apart from that in the lungs.[18]

Furthermore, in a study which used a multi-center database, data from the ELSO registry were analyzed separately for the entire time period and recent years (between 2002 and 2006). This study revealed that advanced patient age, increased pre-ECMO ventilation duration, diagnosis class, and complications during ECMO were associated with mortality.[19] Another study found that advanced age, renal and multi-organ failure, and the necessity of a high minute ventilation were the predictors of ECMO mortality. Additionally, the best outcome was noted in trauma patients.[16] In our study, we found no predictive factor for ECMO mortality, possibly due to small sample size.

In the majority of studies, the first option for cannulation was described as the right femoral vein for drainage and right internal jugular vein for return. Particularly in a study, the cannulation sites were standardized by Ganslmeier et al.[20] with the right femoral vein being used for drainage and the right internal jugular vein serving to return the arterialized blood. However, we mostly used bifemoral veins for cannulation in our patients (24/33). We considered some factors for the selection of bifemoral veins. First, we were unable to use the jugular veins in a large proportion of patients, due to the central intravenous catheters or hemodialysis catheters hindered placement of the return cannula. Second, the combination of positioning therapy and ECMO support was unable to be occasionally suitable, while there was a cannula at the right or left jugular region. Lung recruitment and oxygenation may be improved by positioning therapy, and this therapy modality should be a part of the standard care in severe ARDS.[21,22] Third, bifemoral vein cannulation was easily accessible without worsen flow properties and kinking; therefore, we experienced no problem related to the pump flow in our patients.

In addition, complications associated with ECMO in patients with ARDS are directly related to the ECMO circuit, while some others are indirectly related. The common direct complications are the oxygenator failure, blood clots in oxygenator and other circuit, and cannula-related problems, whereas indirect complications are bleeding in the surgical or cannulation site, pulmonary, gastrointestinal, or intracranial region, hemolysis, arrhythmia, disseminated intravascular coagulation, and culture-confirmed infections at any site.[23,24] Our complication rates during the ECMO support were within an acceptable range. Bleeding

complications at the cannulation sites were most common and usually managed through mild pressure, and surgical revision was not necessary, except one case. However, despite systemic heparinization, DVT developed in three patients and the incidence of DVT (9.1%) was higher compared to the previous studies. The higher incidence of DVT can be attributed to the bifemoral venous cannulation, as bifemoral venous cannulation may cause more stasis in lower extremity venous circulation.

Additionally, transfusion requirements were mostly related to the overall condition of the patients, rather than hemolysis by the centrifugal pump. The main cause of mortality was multi-organ failure, but not hypoxemia and hypercapnia.

On the other hand, ECMO is costly and labor-intensive. In the CESAR trial, the mean cost per patient in the ECMO group was more doubled than the control group (£73,979; $116,502) over a period of six months.[9,25] Therefore, the patient selection for ECMO is of utmost importance for both to reduce the costs and to obtain improved outcomes. The creation of an appropriate standardized protocol may provide to improve the outcomes. However, defining the selection criteria for ECMO patients is usually difficult and based on local experience. In our institution, we have applied vv-ECMO to selected patients with ARDS for five years, using an established protocol based on our experience, which makes our institution one of the most experienced centers for ECMO applications in Turkey.

To the best of our knowledge, this study is the first clinical analysis of ECMO for ARDS in Turkey. Nonetheless, it has some limitations. First, ECMO therapy is relatively new in our institution and, hence, our sample size is small. Second, the study design is retrospective, and the study population is not homogeneous. Third, although all patients who were supported with ECMO were carefully selected, a control group was unable to be selected to indicate the superiority of ECMO. Finally, we only considered the survival rate as our primary outcome without any mid- and long-term morbidity of survivors.

In conclusion, venovenous extracorporeal membrane oxygenation is a beneficial and effective supportive therapy, and can be a life-saving treatment modality for carefully selected patients with severe acute respiratory distress syndrome who are refractory to conventional therapies. Improved results may be provided with increased experience and an established standard protocol for the management of venovenous extracorporeal membrane oxygenation.

Declaration of conflicting interests

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