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Early extracorporeal life support experiences in 2 tertiary pediatric intensive care units in Turkey

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Background/aim: Extracorporeal membrane oxygenation (ECMO) is a unique life-support modality offered to patients unresponsive to optimal medical therapy. The aim of this study was to evaluate early experiences with ECMO support in 2 tertiary Turkish pediatric intensive care units (PICUs).

Materials and methods: We retrospectively evaluated a total of 10 ECMO-supported patients between March 2012 and March 2013 in Marmara and Ege University Hospital PICUs. We reported data regarding demographics, laboratory and diagnostic information, and the clinical course of the patients.

Results: The study consisted of 6 males and 4 females from 5 months to 14 years of age (mean age: 0.5 ± 5.01 years) supported with ECMO. Out of the 10 patients, 8 were on venovenous ECMO for respiratory failure and 2 received venoarterial ECMO for cardiac failure. Mean ECMO and intensive care duration was 11.1 ±7.3 days and 23.5 ±17.8 days, respectively. Bleeding was the most common complication (60%). Forty percent of the patients were weaned from ECMO, among which 50% were discharged in good health without sequelae.

Conclusion: Initial experiences build the learning curve of institutions, and our early results are encouraging. Giving time to heal to the right patient at the right time is the key to success.

Key words: Extracorporeal life support, extracorporeal membrane oxygenation, intensive care, pediatric

1. Introduction

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) is a modified form of cardiopulmonary bypass used to provide oxygen delivery in patients with severe respiratory and/or cardiac failure (1). This support is applied to patients with high mortality risk who are unresponsive to optimal medical therapy (2). Generally accepted indications for pediatric respiratory ECMO are: potentially reversible respiratory failure associated with high risk of death without ECMO, acute hypoxemia unresponsive to maximum medical therapy, oxygenation index (OI) of >40 for greater than 2 h, hypercarbic respiratory failure with pH of <7.2, and persistent air leaks on maximum support (3). Cardiac ECMO is mostly used for preoperative stabilization and postcardiotomy support of critical patients with congenital heart disease. Other uses are in severe myocarditis and cardiomyopathies, intractable arrhythmias with hemodynamic compromise, severe pulmonary hypertension, and septic shock. If used during cardiopulmonary resuscitation, this support is called extracorporeal cardiopulmonary resuscitation.

During ECMO, anticoagulated blood drained from the venous circulation is pumped through an artificial lung (membrane oxygenator), where oxygen is added and carbon dioxide is removed, and is returned back to the patient's circulation. If the oxygenated blood is returned to the venous side, it is venovenous (VV), and this is mainly for respiratory support. If it is returned to arterial circulation, it is referred to as venoarterial (VA) support,

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and it can be used both for respiratory and cardiac failure. The first successful use of ECMO was with an adult with acute respiratory distress syndrome (ARDS) after trauma in 1972 (4).

The Extracorporeal Life Support Organization (ELSO), founded in 1989, maintains a registry of ECMO data collected since 1976. According to the 2013 registry data, there are over 200 centers that have cumulatively reported over 55,000 ECMO cases across the globe. Among the cases involving pediatric respiratory problems, 65% of patients survive ECLS and 56% survive to discharge or transfer. These rates for pediatric cardiac ECLS cases are 65% and 49%, respectively.

In Turkey, VA-ECMO experience for perioperative low cardiac output syndrome is accumulating in congenital heart surgery centers and there is a recent interest in ECMO in some tertiary pediatric intensive care units (PICUs) as well (5). As centers with ECMO services, we (Marmara and Ege University Hospital PICUs) pooled our ECMO records to evaluate demographic, technical, laboratory, and outcome data.

2. Materials and methods

We evaluated a total of 10 ECMO-supported patients between March 2012 and March 2013 in the Marmara and Ege University Hospital PICUs and reported data regarding demographics, laboratory and diagnostic information, and clinical courses. We performed descriptive data analysis on the data, using SPSS 16 for statistical calculations. We report numerical values in the text as means and standard deviations of the means. We analyzed nonparametric data with Mann–Whitney tests and parametric data with Pearson tests.

3. Results

Each institution had 5 patients supported with ECMO (6 males and 4 females), with ages from 5 months to 14 years (mean: 4.5 ± 5.01 years). Patient demographics and medical descriptive data are given in Table 1. Most patients were moribund before the initiation of ECMO, with 1 patient being cannulated under active resuscitation. Inotropic support was necessary in 90% of cases. Mean doses of inotropes in $\mu g\ kg^{-1}\ min^{-1}$ before and after ECMO were as follows: dopamine, 12.5 ± 2.89 versus 13.75 ± 4.79; epinephrine, 1.15 ± 1.20 versus 0.57 ± 0.95; milrinone, 0.42 ± 0.14 versus 0.41 ± 0.14; norepinephrine, 0.17 ± 0.05 versus 0.15 ± 0.04. Out of the patients, 60% had comorbidities.

Eight patients were on VV-ECMO for respiratory failure and 2 patients received VA-ECMO for cardiac failure. Patients with respiratory failure had a mean OI of 44.4 ± 16.3 and a mean partial arterial oxygen pressure/fractional inspired oxygen ratio (PaO_2/FiO_2 ratio: P/F ratio) of 64.6 ± 37.0. ECMO support was initiated within 48 h of PICU admission in 60% of cases. Ventilation methods and parameters with arterial pH and lactate levels before and after ECMO within 24 h are listed in Table 2. With ECMO support, mean pH increased from 7.13 ± 0.23 to 7.43 ± 0.09 (P = 0.005), and mean lactate level decreased from 5.76 ± 4.55 mmol/L to 2.79 ± 2.03 mmol/L, but this decrease was not statistically significant (P ≥ 0.05).

Technical ECMO data are given in Table 3. Patients whose ventilator FiO_2 requirement decreased below 0.45 were able to be weaned from ECMO support (n = 4). Half of the weaned patients (n = 2) were discharged in good health without sequelae. One of the survivors was discharged from the PICU, and the other from a regular floor 10 days after transfer from the PICU. The remaining half died due to sepsis and underlying comorbidities on days 10 and 11 after the removal of ECMO support. None of the cardiac ECMO patients were able to be weaned from the support.

Bleeding was the most frequent complication (60%). Although this was mostly (40%) observed at the catheter insertion site, which was easy to control with local pressure, 2 patients (20%) had major bleeding necessitating cessation of heparin. Among patients, 30% had their oxygenator changed. Renal replacement therapy for acute kidney injury was performed in 30% of cases, and 1 of those patients had continuous VV hemodialysis for severe hypernatremia. Plasma exchange was done due to hemolysis in 1 patient (10%). Air leaks (pneumothorax, pneumomediastinum, subcutaneous emphysema) were present in 50% of the cases before initiation of ECMO. Drainage of air was necessary for 2 patients (20%) with pneumothorax and 1 with pneumoperitoneum during ECMO support. After drainage of pneumothorax, 1 patient with immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) developed a massive hemothorax and a growing hematoma at risk for compartment syndrome in the upper extremity brachial region. After we discontinued heparin, we drained the massive hematoma in the left hemithorax via a minithoracotomy, and we successfully weaned the patient from ECMO. The risk of compartment syndrome of the upper arm was resolved with conventional measures.

4. Discussion

ECMO can be an aid to sustain life in refractory respiratory and/or circulatory failure until the cause can be found and treated. In newborns and adults its efficiency has been shown in randomized controlled studies (6,7). Pediatric evidence comes from a large multicenter study (8).

Our series included 8 patients who received VV support for respiratory failure. Commonly used oxygenation parameters for ECMO evaluation include P/F ratio and

Table 1. Patient demographics and medical descriptive data.

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean	SD
Age (years)	0.58	0.41	4.00	1.50	0.58	2.00	4.00	14.00	5.00	13.00	4.51	5.01
Weight (kg)	7	8	15	9	7	15	17	51	20	45	19.40	15.79
Sex	Male	Female	Male	Female	Male	Female	Male	Male	Female	Male		
ECMO reason	ARDS, pneumonia	ARDS, air leaks, cardiopulmonary arrest	ARDS	ARDS, RSV pneumonia, sepsis	LCOS	ARDS	ARDS, pneumonia, sepsis	LCOS	ARDS, varicella pneumonia	Hydrocarbon aspiration pneumonitis	NA	NA
Comorbidities	BPD	NA	IPEX syndrome	ALL, pancytopenia	TOF	NA	ALL	Dilated CMP	NA	NA	NA	NA
PIM2 (%)	8.60	13.1	8.80	74.60	39.70	66.00	50.00	30.00	15.00	9.30	31.51	24.95
PRISM 2 score	11	6	3	24	20	16	6	14	21	6	12.7	7.41
PELOD score*	20	12	21	21	54	31	21	12	21	20	23.3	12.02
ECMO start (day)	18	1	13	2	1	1	2	1	10	13	6.20	7.85
ECMO duration (days)	14	7	15	18	1.25	0.04	1	15	29	11	12.36	7.33
ECMO weaning	No	Yes	Yes	Yes	No	No	No	No	No	Yes	NA	NA
Discharge status	Exitus	Alive	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Alive	NA	NA
PICU days	32	26	37	30	1.25	0.58	3	15	40	51	23.58	17.78

PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, BPD: bronchopulmonary dysplasia, ALL: acute lymphoblastic leukemia, TOF: tetralogy of Fallot, RSV: respiratory syncytial virus, CMP: cardiomyopathy, LCOS: low cardiac output syndrome, SD: standard deviation, *: PELOD on ECMO start day. The initial 5 patients are from Marmara University; the remainder are from Ege University.

Table 2. Ventilation and oxygenation parameters before and after ECMO.

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Ventilation before ECMO	P-SIMV F: 60 PIP: 38 PEEP: 17 FiO2: 1.0 MAP: 30	P-SIMV F: 60 PIP: 30 PEEP: 10 FiO2: 1.0 MAP: 20	P-SIMV F: 40 PIP: 34 PEEP: 14 FiO2: 1.0 MAP: 28	HFOV FR: 3.7 IT: 35 AMP: 45 FiO2: 1.0 MAP: 38	P-SIMV F: 60 PIP: 25 PEEP: 6 FiO2: 0.5 MAP: 16	P-CMV F: 25 PIP: 30 PEEP: 7 FiO2: 1.0 MAP: 18	P-CMV F: 20 PIP: 32 PEEP: 8 F iO2: 1.0 MAP: 19	APV-CMV F: 16 PIP: 19 PEEP: 5 FiO2: 0.45 MAP: 10	APV-CMV F: 30 PIP: 45 PEEP: 10 FiO2: 0.90 MAP: 26	P-CMV F: 24 PIP: 38 PEEP: 8 FiO2: 1.0 MAP: 21
Ventilation during ECMO (first 24 h)	P-SIMV F: 20 PIP: 20 PEEP: 10 FiO2: 0.60	P-SIMV F: 10 PIP: 24 PEEP: 8 FiO2: 0.25	P-SIMV F: 20 PIP: 21 PEEP: 8 FiO2: 0.50	HFOV F: 5.5 IT: 35 AMP: 35 MAP: 27 FiO2: 0.40	P-SIMV F: 20 PIP: 22.5 PEEP: 5.5 FiO2: 0.40	P-CMV F: 25 PIP: 30 PEEP: 7 FiO2: 1.0	P-CMV F: 12 PIP: 30 PEEP: 8 FiO2: 1.0	APV-CMV F: 10 PIP: 24 PEEP: 6 FiO2: 0.35	APV-CMV F: 10 PIP: 40 PEEP: 5 FiO2: 0.85	P-CMV F: 10 PIP: 20 PEEP: 6 FiO2: 0.45
P/F	43.9	44	67	58.2	92	44	50	377	154	56
OI	68.3	45.4	41.7	65.2	17.39	41	38	3	17	38
Lactate 1 (mmol/L)	2	11	3.7	5.1	10	5.1	1.6	14.5	0.8	3.8
Lactate 2 (mmol/L)	6	2	2	1.6	6	5	1	1.3	1.1	1.9
pH 1	7.15	6.75	6.96	7.08	6.86	7.23	7.48	7.27	7.09	7.47
pH 2	7.43	7.33	7.44	7.40	7.34	7.30	7.55	7.46	7.55	7.54

P-SIMV: Synchronized intermittent mechanical ventilation pressure controlled, F: frequency, PIP: peak inspiratory pressure, PEEP: positive end expiratory pressure, FiO2: fractional inspired oxygen, MAP: mean airway pressure, HFOV: high-frequency oscillatory ventilation, P-CMV: pressure controlled mechanical ventilation, APV-CMV: adaptive pressure ventilation-controlled mechanical ventilation, lactate 1 and pH 1: lactate and pH before ECMO initiation, lactate 2 and pH 2: best lactate and pH after ECMO support within 24 h.

Table 3. Technical ECMO data.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
ECMO modality	VV	VV	VV	VV	VA	VV	VV	VA	VV	VV
Cannula site	RIJV + RFV	RIJV	RIJV + RFV	RIJV + LFV	RA-aorta	RIJV + RFV	RIJV + RFV	LFV, RFA	RIJV + RFV	RIJV + RFV
Cannula size (French)	13 dl + 8	15 dl	18 dl + 12	18 dl + 10	18 + 10	8 + 12	17 + 14	18 + 16	18 dl + 15	19 + 17
Maximum blood flow*	100	106	100	140	142	107	47	88	50	78
Circuit change	Yes	No	No	Yes	No	No	No	Yes	Yes	No
Cannula brand	OriGen MDLP	OriGen	OriGen MDLP	OriGen MDLP	MDLP Medtronic	Maquet	Maquet	Maquet	Maquet Novolung	Maquet
ECMO system**	Medos	Maquet	Maquet	Maquet	Maquet	Maquet	Medos	Maquet	Maquet	Maquet

VV: Venovenous, VA: venoarterial, RIJV: right internal jugular vein, RFV: right femoral vein, RA: right atrium, LFV: left femoral vein, RFA: right femoral artery, dl: double lumen catheter, MDLP: Medtronic DLP cannula, *: blood flow in mL kg^{-1} min^{-1}. **: Maquet systems used Quadrox ID and Medos systems used Medos Hilite oxygenators; integrated ECMO heat exchangers were used. Continuous renal replacement therapies in selected patients were performed via Prismaflex system with appropriate hemofiltration filters.

OI. Historically, an OI of >40 predicted a mortality rate of 80%, whereas 25 < OI < 40 predicted a 50%–80% mortality rate (9). In pediatric respiratory failure with OI of >40, even 6 h of ventilation was associated with a mortality rate of 40% with increasing risk over time (10).

Our patients with respiratory failure had an average OI of 44.3 ± 16.0 before initiation of VV-ECMO. Since they had received the maximum available support before ECMO, imminent death was expected. In particular, a 5-month-old with ARDS and massive air leaks was put on ECMO support under active resuscitation; as far as we know, this patient became the first infant survivor of VV-ECMO for respiratory indication in a Turkish PICU. Patients who were successfully weaned from ECMO had significantly lower FiO_2 requirements from the ventilator during ECMO support compared to those who failed to wean (0.40 ± 0.10 versus 0.86 ± 0.19; P = 0.005). In our series, 1 patient with dilated cardiomyopathy was bridged to transplant. Unfortunately, the patient expired before transplant. The most common complications were bleeding (60%) and inadequate flow requiring additional cannulation (50%). Bleeding was mostly at the cannulation sites, which was easily controlled with local pressure. Anticoagulation was discontinued in 2 patients due to uncontrollable bleeding. According to the ELSO 2013 registry report, the most common complications in respiratory ECMO are bleeding around the cannulae (16.8%), cannulae problems (15%), bleeding at the surgical site (13%), oxygenator problems (12.3%), and hemolysis (9.8%); cardiac ECMO is associated mostly with persistent need for inotropic support (59.5%), bleeding at the surgical site (31.4%), and the need for hemofiltration (25.8%).

Protective lung ventilation decreases ventilator-induced lung injury and hence improves the outcome (11). The size and insertion site of cannulae is extremely important for reaching adequate blood flows and to provide adequate oxygenation so that the lungs can rest. The initiation of ECMO was mostly under impending arrest conditions in our patients. Therefore, cannulation safety and pace was extremely important. All patients were cannulated by a local cardiovascular surgery team at the bedside. At Marmara University, the average time between the decision and ECMO support was 2 h, whereas at Ege University, this was around 6 h. The delay in obtaining appropriately sized cannulae was the reason for later initiation of ECMO at Ege University. We acknowledge that this delay may have caused secondary myocardial injury with poor outcomes as a result in 2 patients. Hence, we want to emphasize the need for full equipment with backups on standby for use in reference centers.

The cost of this potentially life-saving support therapy is acceptable when compared with conventional therapy

for the critically ill. A 5-month-old infant with ARDS and massive air-leak syndrome was billed 46,000 Turkish lira for a 27-day PICU stay. This patient has a full life expectancy. In adult and neonatal respiratory failure, the cost-effectiveness of ECMO compared to conventional therapies is proven (7,12).

In our study, 4 out of 8 respiratory ECMO patients (50%) were successfully weaned; 2 of them survived without disability. To our knowledge, in addition to our patients, a total of 8 other pediatric ECMO patients were supported in 4 other Turkish university hospital PICUs as of August 2013, mostly (75%) in VA mode. Of those patients, cumulative weaning rate was 37% and survival rate 25%. ELSO data on pediatric patients with respiratory problems report a weaning success rate of 65% and survival rate of 56%. Our early experiences with ECMO have helped our learning curve and are encouraging with regards to the feasibility and success of the procedure. The Marmara University PICU became the first Turkish medical center to join the ELSO in 2012. ELSO guidelines and data-sharing helped us in organizing and preparing our multidisciplinary teams and managing our patients. We expect our success rates to go up as equipment and supplies for the procedure are optimized and our multidisciplinary team approach is maintained. The team must be well rehearsed in emergency responses. Complications are common and preparation and proper response in cases of system failure are of paramount importance. The number of ECMO procedures conducted by a medical center is correlated with the success rate (13,14). Experienced personnel, appropriate patient selection, constant availability of ECMO equipment, short cannulation times, and establishment of ECMO referral centers are all factors that affect the ECMO success rates.

ECMO support is in its infancy in Turkey. Our preliminary experiences helped us build our learning curve, and our early results are encouraging. With better patient selection, timing, readiness of ECMO equipment, and fully trained staff, we are hopeful that our success rates will grow.

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