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Venoarterial extra corporeal membrane oxygenation experience in pediatric patients

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Abstract

Aim: Extracorporeal membrane oxygenation (ECMO) is a life-saving strategy in pediatric patients when faced with cardiac or respiratory failure after cardiac surgery. In this article, we investigated the relationship between mortality and data, such as leukocyte, hematocrit (HCT), blood urea nitrogen (BUN), creatinine (CRE), albumin, lactate, c-reactive protein (CRP), systemic immune-inflammation index (SII), platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lactate- albumin ratio (LAR) which can be easily calculated from daily routine complete blood count and biochemistry tests of ECMO patients.

Materials and Methods: We obtained hospital records of 12 pediatric and newborn patients who needed ECMO therapy. The patients were divided into two as non-survivors (Group NS) and survivors (Group S). Factors that may affect mortality were investigated.

Results: Four patients (33%) were successfully weaned from ECMO and discharged. The remaining 8 patients died. 50% of the patients were male (n=6). While the median age was 28 (4-275) days in Group NS, the median age was 300 (300-960) days in Group S. Although not statistically significant (p=0.395), patients with younger age had a higher mortality rate. While the mean weight was 5.9±3.2 kg in Group NS, it was 6.9±3.2 kg in Group S. Postoperative PLR, SII in Group NS were higher compared to Group S. There was no statistically significant difference between the two groups. Bleeding rate was higher in Group NS than in Group S. There was an increase in postoperative NLR in Group NS compared to preoperative NLR.

Conclusion: Although postoperative PLR and SII were found to be higher in Group NS, postoperative NLR was increased compared to preoperative NLR, and bleeding complications were more common in group NS, none of these parameters reached a statistically significant level.

Introduction

ECMO is a life-saving strategy in pediatric patients when faced with cardiac or respiratory failure after cardiac surgery. ECMO was first used in neonates in the 1970s and was first successfully used by Dr Robert Bartlett in 1975 in a newborn with meconium aspiration syndrome who did not respond to medical therapy, and the patient was successfully weaned from ECMO [1]. Later, it started to be used in adult patients over time. After the promising success of Dr. Barlett, use of ECMO has gradually increased with the developing technology and has been supported by many clinical studies [2,3]. ECMO support can be used for pulmonary or both pulmonary and cardiac support. It is used for supportive treatment, not for therapeutic purposes. Therefore, when determining the need for ECMO, it is important for the patient to have a reversible pathophysiology in terms of ECMO success [4]. ECMO, a modified version of the cardiopulmonary bypass circuit, is also called extracorporeal life support (ECLS).

The venous blood taken from the patient is transferred to the membrane oxygenator for oxygenation and gas exchange, and then the oxygen-rich blood is transferred back to the arterial or venous system by centrifugal or roller pump head. If the blood is transferred back to the venous system, it is called venovenous, if it is transferred to the arterial system, it is called venoarterial ECMO. ECMO experience comes mainly from the pediatric and neonatal

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population since the success rate of ECMO is lower in the adult population.

The purpose of ECMO is to ensure the continuity of end-organ perfusion and oxygenation until the underlying cause is resolved. Therefore, hemodynamics, lactate, acidosis, venous saturation, perfusion, urine output and other organ function parameters that give an idea about oxygenation should be closely monitored. In our clinic, these and other patient parameters are evaluated daily by a large team including pediatric cardiac surgeon, pediatric cardiologist, pediatric intensive care doctor, perfusionist, and patient's nurse.

By the contact of the blood coming from the patient with the foreign surface of ECMO, pro-coagulant and pro-inflammatory mediators are activated in the blood [5]. Changes in the proportions of cellular components in peripheral blood can provide insight into many diseases and sometimes prognosis of the patient. In addition to being valuable in the follow-up of individuals with heart failure, PLR and NLR have also been associated with mortality and morbidity in cardiac patients [6,7].

In this article, we investigated the relationship between mortality and data, such as leukocyte, HCT, BUN, CRE, albumin, lactate, CRP, SII (neutrophil count × platelet count) / lymphocyte count), PLR, NLR, LAR which can be easily calculated from daily routine complete blood count and biochemistry tests of ECMO patients [6,7].

Materials and Methods

After the approval of the Ethics Committee of our hospital (University of Health Sciences Diyarbakır Gazi Yasargil Training and Research Hospital Ethics Committee, date: 24/06/2022 number: 120), we obtained hospital records of 12 pediatric and newborn patients who needed ECMO, who were operated by the same surgeon in our hospital between October 2020 and April 2022. Intraoperative bypass and cross clamp times of the patients, postoperative mechanical ventilation time, high flow nasal cannula (HFNC) time, ECMO length of stay, preoperative and postoperative platelet, leukocyte, lymphocyte, neutrophil, HCT, CRP, albumin, lactate, urea, CRE values, postoperative complications, mortality, successful seperation of ECMO were evaluated.

In ECMO treatment, it is aimed to provide end-organ and myocardial perfusion. Left ventricular end-diastolic pressure is lowered by draining blood from the patient circulation into the ECMO circuit. Thus, the perfusion of the myocardium is increased.

Determining indications for initiating extracorporeal support in the pediatric patient is a constantly changing and expanding field. Most information on the use of ECMO comes from the Extra-corporeal Life Support Organization (ELSO) international database and guidelines on the ELSO website.

In our cohort, all patients underwent veno-arterial ECMO. One patient received peripheral ECMO, while all remaining patients underwent central ECMO. In emergencies, patients were cannulated in the intensive care unit, while non-emergency patients were cannulated in the operating room. Single artery and single venous cannula were used for cannulation. In intraoperative ECMOs, it was generally preferred to switch to ECMO with existing cannulas. Patients underwent ECMO mainly due to the inability to wean from cardiopulmonary bypass after cardiac surgery, ventricular dysfunction and low cardiac output after cardiac surgery. Blood was routinely used to prime ECMO. ACT was followed up during ECMO and heparin infusion was started with an ACT between 160 and 200. The flow of ECMO was set at 100-150 ml/kg/min. Ventilation parameters were decreased to resting values such as FIO2 = 0.21 to 0.3, tidal volume 4-6 ml/kg, frequency 12-18/min, and PIP/PEEP 20/8. The hematomas that developed in patients who stayed in ECMO for a long time were cleared regularly. The patients were divided into two groups as Group NS and Group S. Factors that may affect mortality were investigated.

Statistical analysis

Data was analyzed through the SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)) package program. Continuous variables (Age, ICU duration, Weight, etc.) were expressed as mean ± standard deviation. Median (minimum-maximum) and qualitative variables (Renal failure, Bleeding, Ventricular Dysfunction, etc.) were expressed as number (percentage). The Chi-square analysis (Pearson Chi-square) was used to compare intergroup categorical variables. Shapiro Wilk test was used for the normality analysis of the data. In independent group comparisons, the variance analysis and significance test of the Student t test between the two means were used when parametric test assumptions were provided. Mann–Whitney U test was used when parametric test assumptions were not provided. A p-value <0.05 was considered statistically significant.

Results

In our cohort while four patients (33%) were successfully weaned from ECMO and discharged, the remaining eight patients died. 50% of the patients were male (n=6).

Rastelli operation was performed in one patient with the diagnosis of ventricular septal defect and pulmonary atresia. Central venoarterial (VA) ECMO indication was due to the inability to wean from cardiopulmonary bypass (CPB). She was weaned from ECMO in the intensive care unit on the third postoperative day and she was discharged on the 24th postoperative day. Arrhythmia-related arrest developed in one patient during the extubated intensive care follow-up after permanent pacemaker implantation. Cardiopulmonary resuscitation (CPR) was performed, and then ECMO- CPR (ECPR) was performed in the intensive care unit. The patient died on the second day of ECMO. Biventricular repair was performed in another patient with a diagnosis of hypoplastic left heart syndrome who underwent Norwood Stage I, since both ventricles were well developed in the follow-up. The patient, who developed acute respiratory distress syndrome (ARDS) like symptoms on the first postoperative day, underwent central ECMO in the intensive care unit. Patient was weaned from ECMO in the intensive care unit on the seventh postoperative day and was discharged on the 46th

Table 1. Comparison of parameters based on ECMO results.

	Nonsurvivors (n=8)	Survivors (n=4)	p-value
Age (day) (median,min-max)	28 (4-275)	300 (300-960)	0.395[a]
ICU duration (day) (mean±SD)	20.6±13.4	67.3±68	0.041*[b]
Weight (kg) (mean±SD)	5.9±3.2	6.9±3.2	0.730[b]
Ventilatorduration (day) (mean±SD)	19.8±14.4	56.7±75.7	0.734[b]
(median, min-max)	11(7-40)	17(9-144)	
Duration of HFNC (median, min-max)	0(0-0)	3 (0-7)	0.007*[a]
Duration of ECMO (day) (median, min-max)	8(3-40)	6(4-7)	0.608[a]
CPB time (min) (mean±SD)	124.3±88	143±184	0.883[b]
Clamp time (min) (mean±SD)	245±137	289±270	0.819[b]

Data are means±SD, medians and ranges or numbers. p< 0.05 is considered clinically significant. [a]: Mann Whitney U, [b]: Student t test was used. CPB: cardiopulmonary bypass ,ECMO: extracorporeal membrane oxygenation, HFNC: high flow nasal cannula.

postoperative day. A five month old patient who developed ARDS-like symptoms due to COVID-19 underwent peripheral ECMO in the operating room. After eight days, patient was weaned from ECMO in the intensive care unit and was discharged 32 days later. This was also one of the youngest patients in the literature to be successfully weaned from ECMO due to COVID-19 and discharged. Double-switch (Rastelli+Senning) surgery was performed in one patient due to c-TGA (corrected-Transposition of great arteries)+VSD (Ventricular septal defect)+LVOTO (left ventricular outflow tract obstruction). The patient who could not wean from CPB was transferred to the intensive care unit with central ECMO support. The patient died on the 40th postoperative day. Double-switch (Senning + Arterial switch) operation was performed for c-TGA in another patient. Due to low cardiac output, the patient was transferred to the intensive care unit with central ECMO support. Patient was lost on the 23rd postoperative day. A patient with TGA, unbalanced AV(atrioventricular) canal, and pulmonary stenosis underwent central ECMO due to the development of low cardiac output after central shunt operation. Patient was weaned from ECMO on the fourth postoperative day and was discharged on the 203rd postoperative day. Another patient who developed low cardiac output after hypoplastic arcus repair, atrial septectomy and pulmonary banding underwent central ECMO. The patient died on the eighth postoperative day. A patient who was operated with the diagnosis of TGA after septostomy underwent central ECMO due to failure to wean from CPB. Patient died on the 29th postoperative day. E-CPR was applied to the patient who underwent pulmonary reconstruction, central shunt, and septectomy with the diagnosis of VSD, pulmonary atresia, and mitral atresia, because of cardiac arrest at the postoperative follow-up. The patient underwent ECMO and died on the ninth postoperative day. The patient, who underwent arcus repair and pulmonary banding with the diagnosis of TGA, DILV (double inlet left ventricle), VSD, arcus hypoplasia underwent central ECMO due to failure to wean from CPB. Patient died on the 40th postoperative day. A patient who underwent Norwood procedure with the diagnosis of hypoplastic left heart syndrome underwent ECMO due to the failure to wean from CPB. Patient died on the ninth postoperative day.

While the median age was 28 (4-275) days in Group NS, the median age was 300 (300-960) days in Group S. Although not statistically significant (p=0.395), patients with younger age had a higher mortality rate. While the mean weight was 5.9±3.2 kg in Group NS, it was 6.9±3.2 kg in Group S. In Group NS, the length of stay in the intensive care unit was less than Group S and it was found to be statistically significant (20.6±13.4 days, 67.3±68 days, p=0.041, respectively). Although not significant, ECMO duration in Group S was lower than Group NS. There was no significant difference between the CPB duration and cross clamp duration of the two groups (Table 1).

When the preoperative and postoperative laboratory values of Groups NS and S were examined, only postoperative CRP and BUN were found to be significantly higher in Group S. In the literature, among the parameters associated with mortality and prognosis, such as preoperative and postoperative NLR, PLR, LAR, SII only postoperative PLR and SII in Group NS were higher compared to Group S. There was no statistically significant difference between the two groups [8-10] (Table 2).

When both groups were compared in terms of postoperative complications, two patients in each group required peritoneal dialysis. Bleeding complications associated with coagulation anomalies and anticoagulant therapies during ECMO support requiring blood transfusion were seen in 2 patients in Group NS. Although it was not statistically significant, bleeding rate was higher in Group NS than in Group S. Epileptic seizure was observed in one patient in Group S and antiepileptic treatment was started. In Group NS, neurological findings developed in the patient who underwent E-CPR after CPR. One patient in Group S was discharged with tracheostomy. Sepsis developed in one patient in Group NS and in two patients in Group S (Table 3). Six of the twelve patients were successfully weaned from ECMO, while four of these patients were discharged.

Discussion

Based on the international registry of ELSO the use of ECMO has gradually increased, exceeding 55,000 patients only in the pediatric patient group [11,12]. ECMO has an important place in postoperative pediatric cardiac surgery and the prognosis varies from patient to patient. In our study, we investigated the relationship with mortality of these markers, such as PLR, NLR, CRP, SII, LAR which

Table 2. Comparison of values based on ECMO results.

		Nonsurvivors (n=8) (mean±SD)	Survivors (n=4) (mean±SD)	p-value[a]
Number of leukocyte (x10^3/ml)	Initial	11148± 2976	12000±3032	0.396
	Day-1	6002±1947	7750±3391	0.865
Number of neutrophils (x10^3/ml)	Initial	5268±2448	8557±3302	1
	Day-1	4248±1913	5217±2130	0.734
Number of lymphocyte(x10^3/ml)	Initial	4010±3094	3188±3699	0.126
	Day-1	1110±489	1133±284	0.610
Hemoglobin (g/dl)	Initial	13.7±1.3	14.6±3.5	0.865
	Day-1	12.7±1.3	12.8±1.7	0.671
HCT (%)	Initial	42.8±5.2	45.5±9.6	0.497
	Day-1	37.7±3.5	38.5±4.8	0.734
Number of platelet (/L)	Initial	207800±131125	245000±95262	0.734
	Day-1	80200±90270	24833±12770	0.269
NLR	Initial	2.3±1.9	4.1±5.07	0.734
	Day-1	4.9±3.9	5.01±2.6	1
PLR	Initial	43.2±26	138.5±87	0.174
	Day-1	156.5±152.2	23.5±16.3	0.308
SII	Initial	473±283	1343±1009	0.497
	Day-1	349±314	124±101	0.497
BUN (mg/dl)	Initial	18.4±9.1	26±12	0.306
	Day-1	19.8±5.3	37±2.6	0.011
Creatinine (mg/dl)	Initial	0.58±0.24	0.65±0.09	0.610
	Day-1	0.62±0.14	0.77±0.20	0.202
CRP (mg/L)	Initial	6.8±6.6	2.5±0.8	1
	Day-1	15±12.4	46.2±34	0.023
Lactate(mmol/L)	Initial	2.3±1.03	2.2±1.5	0.776
	Day-1	3.06±1.9	5.5±4.1	0.865
Albumin(g/dl)	Initial	2.8±0.3	2.9±0.6	0.302
	Day-1	2.1±0.32	2.9±0.8	0.607
Lactate/albumin	Initial	0.9±0.41	0.8±0.6	0.635
	Day-1	1.3±0.7	2.3±2.1	0.932

Data are means±SD or numbers. p< 0.05 is considered clinically significant.aStudent t test was used. HCT: hematocrit, NLR:Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammatory index; BUN: Blood urea nitrogen.

were found to be associated with mortality, heart failure, sepsis, and inflammation in pediatric patients who needed urgent or postoperative ECMO [13-17].

There are publications in the literature that systemic inflammation, which has an important effect in critical diseases, is also responsible for the poor prognosis in ECMO patients [18]. Yost et al. reported a relationship between NLR and ECMO survival in adult patients [19]. In our study, although there was an increase in postoperative NLR in Group NS compared to preoperative NLR, no statistically significant difference was found between preoperative and postoperative NLRs between Group NS and Group S. Roth et al. also stated NLR as an early prognostic factor for patients in ECMO and associated values above 13 with poor prognosis [20].

There are also publications in the literature stating that there is no significant relationship between PLR and hospital mortality and prognosis in ECMO patients [20,21]. In our study, preoperative PLR was found to be lower in Group NS compared to Group S and there was an increase in postoperative PLR of Group NS. However, no significant difference was found between the two groups (Group NS and S) in terms of PLR values.

Albumin, which is a negative acute phase reactant, decreases in pediatric patients with critical illnesses such as sepsis and metabolic disease. Serum lactate level is a positive acute phase reactant. LAR is a more specific prognostic factor compared to lactate and albumin levels individually [17]. In our study, however, no significant difference was found between the preoperative LARs, and although the postoperative LAR was lower in Group NS compared to Group S, it was not statistically significant.

Pieri et al. stated that CRP can be used as a marker in the diagnosis of infection, especially when combined

Table 3. Postoperative complications.

Complications	Nonsurvivors (n,%)	Survivors (n,%)	P[a]
Renal failure, Peritoneal Dialysis	2(25%)	2(50%)	<0.001
Bleeding	2(25%)	0	0.273
Ventricular Dysfunction	2(25%)	1(25%)	1
Infection, Sepsis	1(12.5%)	2(50%)	0.157
Seizures	1(12.5%)	1(25%)	0.584
Tracheostomy required	0	1(25%)	0.140

p< 0.05 is considered clinically significant. [a]: Chi-square analysis was used.

with procalcitonin in veno-arterial ECMO patients [22]. In our study, especially postoperative CRP was found to be significantly higher in Group S compared to Group NS (p=0.023). The reason for this was that the mean intensive care unit stay of Group S was significantly higher than that of Group NS (p=0.041). It was thought that longer stay in intensive care unit caused more interventions and an increased risk of infection, leading to this increase in the surviving patient group.

Systemic inflammation is triggered by the contact of patient blood with ECMO circuit [5]. It was thought that the treatment of this inflammation may lead to a decrease in ECMO mortality and morbidity [23]. Although there was no statistically significant difference between Group NS and Group S in SII measured in our cohort, the mean postoperative SII was found to be lower in Group S.

Our study has some limitations. First of all, the validity and significance level of our results is limited due to the fact that it is a retrospective, single-center study and a limited population could be evaluated. We think that supporting this study with prospective, multicenter and repeated studies with more patients will increase the significance and level of effectiveness of our results.

Conclusion

In our study, we investigated the low-cost and easy-to-obtain systemic inflammatory markers and other factors that are thought to be associated with mortality in the pediatric and neonatal patient group who underwent veno-arterial ECMO predominantly after cardiac surgery. In conclusion, although postoperative PLR and SII were found to be higher in Group NS, postoperative NLR was increased compared to preoperative NLR, and bleeding complications were more common in group NS, none of these parameters reached a statistically significant level. By observing whether this increasing trend will reach a statistically significant level with higher volume, prospective, multicenter studies indicators that may be associated with mortality can be determined in the pediatric patient group who underwent ECMO and more satisfactory results can be obtained in the follow-up and treatment of these patients.

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Conflict of interests

The authors declare that there are no conflicts of interests.

Ethics approval

The study protocol was approved by University of Health Sciences Diyarbakır Gazi Yasargil Training and Research Hospital Ethics Committee (date:24/06/2022, number:120). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient consent statement

Consent was obtained or waived by all participants' parents in this study.

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