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Identified Mortality Factors during Extracorporeal Membrane Oxygenation (ECMO)

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Abstract

Introduction: ECMO mortality direct related variables were evaluated, specifically anti coagulation, Blood Lactate and Central Venous Saturation.

Materials & Methods: Fifty pediatric patients between 0 to 13 years old were included in a retrospective observational cohort study from January 1, 2013 to June 1, 2019 in 321 ECMO Center. Variables included were Activated Coagulation Time, Non-fractionated Heparin dose, ECMO type, ECMO time, Blood Lactate and Venous Saturation.

Results: Increased mortality ($p>0.05$) was not related to anti coagulation, heparin dose and ACT levels according to a Multiple Logistic Regression Model. Globally, 15% mortality was associated to ECMO type, blood lactate and central venous saturation. When variables were analyzed individually, survival in VA ECMO was 70% vs 20-30% survival in VV ECMO. In case of blood lactate, survival was 80% with 2 mmol/L, and survival decreased twofold with progressive increases. Important Central Venous Saturation decreases below 75%, like consecutive 5% decreases, are twofold related with less survival.

Conclusion: This study has evidently demonstrated that Extracorporeal Membrane Oxygenation (ECMO) use involves maximum responsibility in monitoring, along with a multidisciplinary management. Variables related to anticoagulation were not statistically important; 5% mortality was related to ECMO type, blood lactate, and central venous saturation, making mandatory to explore more about patient's systemic perfusion management and hemodynamic m onitoring, and anticoagulation as well, without losing track of its most common complications.

Keywords: Extracorporeal membrane oxygenation, Risk factor, Prognostic factors

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Introduction

Pediatric Intensive Care implies looking for critic patient's wellbeing who suffered acute changes in their physiological and biochemical parameters with a high risk of death [1], this is the description used by Marilyn to define critical care in context.

There are many multidisciplinary therapies, which give and keep wellness to pediatric patient's health, and it is important to mention that ECMO can be a treatment option to treat critical patients refractory to conventional medical treatment. There are few centers in the world with adequate hospital facilities for this technology, and experience in this area has been increasing along with new studies have been done about its use, benefits, adverse effects, patient's mortality. The most questionable aspect of this therapy is high mortality rate related to long and short term ECMO complications, Important questions mentioned by Loren and López in their respective works, on the various complications during the use of ECMO such as clot formation, thrombosis, infections and hemolysis; problems in anticoagulation therapy during ECMO therapy and massive bleeding, all this to list some of the most important [2,3], Similarly, other important authors

such as Hwa Jin and Barton emphasize the time of anticoagulation administration in ECMO, underlying disease, type of ECMO, systemic perfusion parameters and indications for ECMO as part of the risk in patient mortality [4,5]. Finally, Doymaz comments that associating complications from anticoagulation during ECMO with poor systemic perfusion data related to hemodynamic values such as lactate and venous reserve can negatively influence patient survival, increasing mortality considerably [6].

Materials and Methods

This is a retrospective observational cohort study using multiple logistic regression. Fifty neonatal and pediatric patients recorded on ECMO Muguerza Department electronic database from January 1, 2013 to June 1, 2019. Patients without ECMO treatment were excluded and, according to exclusion criteria, pediatric patients suffering critical disease were not included, as well as ECMO use criteria that for some reason ECMO department records were missing which did not have a relationship with mortality or base disease improvement.

This statistical analysis was made using R Comander Kit and R Statistic Analysis. Quartile comparison graphic methods distribution was analyzed, variables are expressed as medium and standard deviation in case of normality, and median and interquartile range in case of no normality. Comparison between measures of central tendency is made using parametric or no parametric statistics depending on their distribution. A distribution different to the normal was identified; hence variables are expressed in terms of median and interquartile range (**Table 1**). Then, a continuous variables comparison was made ranking patients according to their survival using a Mann-Whitney U Test, a non-parametric test (**Table 2**). As exploratory test, a logistic regression model was made with the maximum model:

DEATH = average ACT + average lactate + average U/Kg (non-fractionated heparin) + VSO2 + ECMO total time + initial U/Kg non-fractionated heparin + maximum U/Kg non-fractionated heparin + gender

Variance factor was calculated eliminating variables with results above three. Then, a mathematical model was made using Type II ANOVA Models, reaching a minimal model with all the significant variables.

Table 1 Continuous Variables with abnormal presentation.

Variable	Median	Interquartile range
Average ACT	213	56.7
Average Heparin (av U/Kg)	21	7.7
Average initial U (ds U/Kg)	15	7.75
Maximum U (max. U/Kg)	30	15
AverageLactate	3	2
VSO2	73	9.5
Average Days Age	18	328
ECMO Days	5	3.75

Note: ACT = Activated Coagulation Time; VSO2 = Central Venous Saturation; ECMO = Extracorporeal Membrane Oxygenation

Table 2 Continuous variables comparison with survival. Mann-Whitney U Test.

Variable	Dead	Alive	P Value
Average ACT	231.6	199.7	0.06
Average Lactate	4.8	3.1	0.06
VSO2 (Central Venous Saturation)	71.7	75.03	0.1
U/Kg ds	15.78	17.22	0.4
U/Kg max	32.1	32.3	0.9
U/Kg average	20.4	22.5	0.4
ECMO Days	7.3	5.6	0.2

Note: ACT =Extracorporal Coagulation Time; VSO2 = Central Venous Saturation; U/Kg ds = HNF Initial Units; U/Kg max = HNF maximum units; U/Kg average = HNF average units; ECMO Days = Extracorporeal Membrane Circulation days.

"DEATH = ECMO (VA/VV) + AVERAGE LACTATE + AVERAGE VSO2"

A Non-significant Theorical Model was calculated, making a comparison with the Minimal Model obtained at the end of the modeling, obtaining statically significant differences: **p-value<0.001**. As response variables were categorical and continuous, a multiple logistic regression model was made; significance of the model was evaluated using a common likelihood ratio test with theoretical null model. Final model was significant. The calculation of the generalization was made through the coefficient R2 equal to 0.05, so the mortality is associated to 5% to these final variables: "DEATH = ECMO (VA/VV) + AVERAGE LACTATE + AVERAGE VSO2"

Results

The goal of the study was to identify influence of variables on death of population. Since 2013, a total of 50 neonatal and pediatric patients were recorded, who were treated using ECMO. In demographics, there were 25 female patients (50%) vs 25 male patients (50%); 23 pediatric patients (46%) vs 27 neonatal patients (54%). In pediatric patients, average age range was 31.3 months vs 2.3 days age in neonatal patients; the death average age range was 4 months (124 days) (**Table 3**). In anticoagulation standards, average ACT in pediatric patients was 196 seconds, 224 seconds in neonatal patients, and death average ACT was 233 seconds. Initial heparin units in case of death de average was 15.7 U/Kg, and average maximum units in case of death was 31 U/Kg (**Table 4**).

Average ECMO therapy time was 6 days, 5.4 days for pediatric patientsvs 6.1 days for neonatal patients, and average time of death of 5.7 days. ECMO type used was VA type for 42 patients (84%), 23 were pediatric patients (46%) vs 19 neonatal patients (73%). VV ECMO was used in eight neonatal patients (16%). Mortality was more related to VA ECMO (73%) compared to VV ECMO (27%). On diagnosis, in pediatric group 14 patients underwent ECMO by cardiac disease (48%), 3 patients by respiratory disease (13%), and 6 patients by infectious diseases (26%). Into the neonatal group, 13 patients underwent ECMO by cardiac cause (48%), 13 patients by respiratory disease (48%), and 1 patient by infectious disease (4%). The most mortality related

Table 3 Demographic variables description, gender, age.

Total Patients 50 patients	50 patients	Gender 1.- Male 2.- Female	Age range death
Pediatric	23 (46%)		
Neonatal	27 (54%)		
Dead	19 patients (38%) 6 pediatric (12%) 14 neonatal (26%)	Pediatric: 1.- 4 (21%) 2.- 2 (10.5%) Neonatal: 1.- 6 (31.7%) 2.- 7 (36.8%)	124 days (4 months)

Table 4 Anticoagulation variable description related to mortality.

PATIENTS 50 TOTAL PATIENTS	AVERAGE ACTIVATED COAGULATION TIME	AVERAGE DS U/KG	AVERAGE U/KG MAX
PEDIATRIC	196 sec	17 units	35.3 units
NEONATAL	224 sec	16.3 units	30.5 units
DEAD	233 sec	15.7 units	31 units

Table 5 Variables description related to time, ECMO type and diagnosis.

PATIENTS 50 TOTAL PATIENTS	AVERAGE ECMO TIME	ECMO TYPE	DIAGNOSIS 1. CARDIAC 2. RESPIRATORY 3. INFECTIOUS
PEDIATRIC	5.4 days	VA 46% VV 0%	1. 14 (60%) 2. 2. 3 (13%) 3. 3 6 (26%)
NEONATAL	6.1 days	VA 38% VV 16%	1. 13 (48%) 2. 2. 13 (48%) 3. 3. 1 (4%)
DEAD	5.7 days	VA 14 (73%) VV 5 (27%)	1. 11 (57%) 2. 2. 7 (36%) 3. 1 (7%)

Note: VA = Venous-Arterial, VV = Veno-Venous, ECMO = Extracorporeal Membrane Circulation

Table 6 Hemodynamic Variables description related to mortality.

PATIENTS 50 TOTAL PATIENTS	AVERAGE CENTRAL VENOUS SATURATION	AVERAGE BLOOD LACTATE
PEDIATRIC	73.5 %	3.2 mmo/Lt
NEONATAL	73.5%	4.6 mmo/Lt
DEAD	68%	5.6 mmol/Lt

diagnosis was cardiac disease (57% of deaths) (**Table 5**). In case of Central Venous Oxygenation, the average value related to more mortality was 68% CVO2, and 5.6 mmol/Lt average lactate value as well(**Tables 6-8**). We have a 66 % survival value and 38% in mortality.

Here below statistical analysis results are described using multiple logistic regression.

Figure 1 is an effect representative graphic where ECMO type and its related survival are shown, and we can determine that VA ECMO use increases survival probability compared to VV ECMO, which decreases patient's survival.

Figure 2 is an effect representative graphic presenting central venous SBG blood lactate value and survival relationship. We can determine that as blood lactate increases, survival probability decreases significantly, compared to blood lactate decreasing which is related to higher survival probability.

Figure 3 represents central venous SBG central venous saturation related to survival. We can determine that, when central SVO2 increases, survival probability increases significantly compared to low central SVO2 which is related to lower survival probability.

Discussion

In this study, we recorded 50 patients into the mentioned period. With the obtained results we can discuss that, based on the analysis of the descriptive databasevariables (Table 7-8). Most of patients needed a progressive increase of non-fractioned heparin

Table 7 Continuous variables.

Variable	Name	Description	Category/ Measurement unit	Variable Type
U/Kg ds	Units	Induction dose to start anticoagulation	International Units	Continuous
U/Kg max	Units	Maximum dose needed to induce anticoagulation	International Units	Continuous
U/Kg average	Units	Average dose to induce anticoagulation	International Units	Continuous
ECMO Time	Time	Time of use of anticoagulation therapy	Days	Continuous
Blood Lactate	Lactate	Average numerical value of blood lactate by venous gasometry in ECMO patients	Mmo/Lt	Continuous
Central Venous Oxygen Saturation	SVO2	Average numerical value of central venous oxygen saturation taken from a central access to the heart. It is estimated in percentage	Percentage	Continuous
ACT	Activated Coagulation Time	Average ACT result	Seconds	Continuous
Average age	Days	Average age in days	Days	Continuous

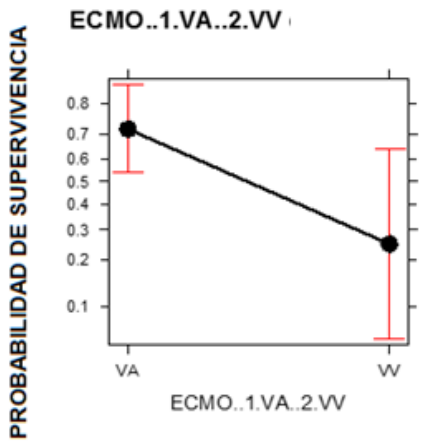

Figure 1 ECMO Type used and survival relationship.

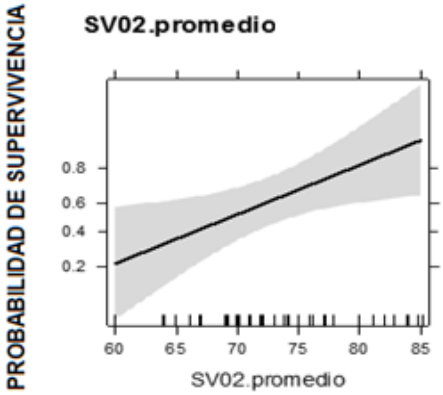

Figure 3 Value of central venous oxygen saturation measured by central venous gasometry and its association with survival.

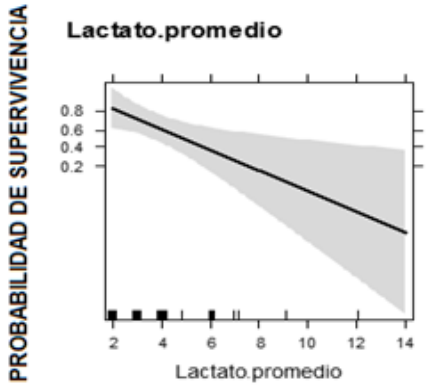

Figure 2 Blood lactate value measured by central venous gasometry and its association with survival.

Table 8 Dichotomous Discrete Variables.

Survival	Death	Dead patients during ECMO Therapy	1 (alive) 2 (dead)	Discrete Dichotomous
ECMO Type	VA ECMO VV ECMO	ECMO type used for support	1. VA 2. VV	Discrete Dichotomous
Diagnose	Cause to start ECMO	Diagnostic reason to start ECMO therapy	1. Cardiac 2. Respiratory 3. Infectious	Discrete Dichotomous

unit/kg dose in continuous infusion to obtain wider ranges of correct anticoagulation, calculated in this study by ACT (Activated Coagulation time). A 213 seconds median was obtained with a 56.7 interquartile range, when we determined ACT in surviving patients (199.7 sec) compared to non-surviving patients (231.6 sec). Mortality did not have a significant p calculated using a Mann-Whitney U Test; p value was 0.06 when we analyzed the

different variables related to patient's anticoagulation under ECMO expressed as average of U/Kg of non-fractioned heparin during ECMO[7-9].

There was no significant statistical difference between non-fractionated heparin, initial and maximum dose units in dead patients (20.4 U/Kg) and surviving patients (22.5 U/Kg), with non-relevant 0.4 p. In terms of ECMO therapy related to non-fractioned heparin time of use, there was no statistical significance as there were patients who died into 7.3 days of therapy vs 5.6 days in surviving patients, obtaining a 0.2 p. This is in contrast to the global literature that according to Cashen documents that the risk of mortality increased by up to 50 to 60% depending on anticoagulation therapy[10]; besides, Hee Lee's study documents an inherent increase in mortality and complications with ECMO use related to anticoagulation itself, reaching 40-80%[11].

There was no significant difference in the use of non-fractioned heparin, including initial, maximum and average doses, as well as any mortality relationship between therapy time and ACT values; with all these, we can relate if the patient would be treated using some type of ECMO therapy.

Anticoagulation protocols used in ChristusMuguerza Alta Especialidad Hospital have shown benefits non related directly to patient's mortality during ECMO. AurunSaini mentions about the difficulty to keep an adequate anticoagulation in ECMO patient with 30-60% more probability of bleeding and deathdeath[12]. Although Roeleveld describes that in pathologies with altered coagulation, between 6 and 30 hours can pass without heparin perfusion in ECMO, but in our study we did not have intrinsic complications of the associated pathology[13].

The aim of this study was to identify the influence of variables on population mortality. Variables themselves did not document some type of statistical significance, but when variables were put into a group a significant model was obtained using the Multiple Logistic Regression Model, showing a 5% mortality related to these final variables.

"**DEATH** = ECMO (VA/VV) + AVERAGE LACTATE * AVERAGE VSO2"

Relationship of patient's mortality, central VSO2 and blood lactate is globally known, and it is mentioned in much type of pathologies in the world. Even, medical training textbooks in Internal Medicine, Pediatrics, Intensive Care, and more, relate SVO2 increase with survival, and blood lactate increase with high mortality[14]; but it is important to mention that nowadays there are no studies documenting direct relationship to survival and the three variables mentioned above in ECMO patients.

According to previous model, we can relate a better survival probability with higher central VSO2, and this probability increases twofold every 5% increase of central SVO2 over 70% central VSO2; in terms of blood lactate, survival probability decreases considerably twofold over 4 mmol/Lt blood lactate, being null survival in case of blood lactate over 10 mmol/Lt.

In world literature, it is well known the relationship between these two variables and its direct effect on mortality. Asenjo describes briefly in his work about the need to improve continuously patient's values of VSO2 and blood lactate during extracorporeal circulation[15], because they might be related to important hypo perfusion and high death risk, but without specifying concrete values on these data. Boedy suggests that mortality is related to high blood lactate and low central VSO2, therefore treatment should focus to improve patient's tissue perfusion monitoring these two variables; as variable values improve, patient's survival would improve[16], but an association variable is not documented, let alone a cut-off number is indicated for patient's improvement, even we know survival should improve, though.

Finally, it is important to note that we could relate ECMO type use to survival, Venous-Arterial (VA) and Veno-Venous (VV). There was a better survival probability using VA ECMO compared to VV ECMO which patients present 4 timer higher probability to die. Nowadays on this area, there are no reports in literature related directly to ECMO type, mortality and survival. According to Ann Arbor and Moreno G, in their respective works, comment on mortality in ECMO therapy, mentioning anticoagulation as a direct factor of mortality, but not associating the ECMO[17,18], but it is important to note that learning curve, heterogeneous diagnoses in pediatric patients requiring ECMO in our hospital might have had some influence, and survival improvement due to a better experience. This is a simple supposition, though, being a high complexity in this moment to relate directly to a specific variable because we only related patients to ECMO type. We still need to determine directly the mortality in each ECMO type, as world literature reports similar characteristics in complications and mortality without predominance of one ECMO therapy over another.

Conclusion

This study demonstrates evidently that Extracorporeal Membrane Oxygenation (ECMO) stands a maximum responsibility in monitoring, surveillance, following and multidisciplinary management for this type of patients.

It was evident in this study that nowadays there is no a significant relationship between anticoagulation used in ECMO patients and mortality, this is in our ECMO team and our experience, even though big success in our surveillance and anticoagulation monitoring scheme used by our team in ChristusMuguerza Alta Especialidad Hospital. But this is not to be taken lightly, because it has been reported a high mortality in patients requiring ECMO, even in the best facilities hospitals in the world, so we should consider multiple complications secondary to anticoagulation in ECMO patients.

Besides, it is an important finding that 5% mortality is related to central VSO2 and blood lactate. It was possible to give evidence as probability in these variables, and give more attention on therapeutic management to systemic perfusion to improve effectively these variables values, and have a direct influence on patient's survival. Another important point is the survival probability related to ECMO types, but we can't still have absolute conclusions on this area because patient's age, different diagnoses and multiple co-morbiditywere not evaluated on this study and they may have some influence on this area, but this cause was not our goal in this study, giving an opportunity for more investigation.

Evaluate our work through a good feedback will give strength to our ECMO Team in ChristusMugherza Alta Especialidad Hospital, and will continue guiding our work to excellence and wellbeing for all our patients.

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