Original Paper

Perfusion

Perfusion
1–9

DOI: 10.1177/0267659117747693
journals.sagepub.com/home/prf
SAGE

Is therapeutic hypothermia during neonatal extracorporeal membrane oxygenation associated with intracranial hemorrhage?

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Abstract

Introduction: The use of therapeutic hypothermia during neonatal extracorporeal membrane oxygenation (ECMO) as a neurologic protective strategy has gained interest among clinicians despite limited data. Our objective is to describe the relationship between the use of therapeutic hypothermia during neonatal ECMO and complications, mortality and functional status among survivors.

Methods: Secondary analysis of data collected by the Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. Data were collected prospectively from 267 neonates (<30 days) undergoing ECMO at eight clinical sites. Twenty neonates received therapeutic hypothermia.

Results: Neonates receiving therapeutic hypothermia were more likely to have intracranial hemorrhage during the first seven days of ECMO than were non-hypothermic neonates (40.0% vs 15.8%, p=0.012). No differences were observed between groups for hospital mortality or functional status at hospital discharge among survivors. Variables independently associated with intracranial hemorrhage in the first seven days of ECMO included therapeutic hypothermia, gestational age at birth, age at initiation of ECMO, fibrinogen concentration and mode of ECMO.

Conclusion: Therapeutic hypothermia during neonatal ECMO appears to be associated with intracranial hemorrhage.

Keywords

therapeutic hypothermia; extracorporeal membrane oxygenation; neonates; intracranial hemorrhage

Introduction

Extracorporeal membrane oxygenation (ECMO) is an invasive form of life support that has been used to treat select groups of neonates with severe cardiorespiratory failure. Studies have shown that ECMO can lead to improved survival compared to conventional management.[1-3] However, long-term complications among survivors, such as neurodevelopmental delay and functional deficits, are common.[3-6] Long-term complications may result from both the underlying disease processes for which ECMO was initiated as well as from the use of ECMO itself.

Therapeutic hypothermia has been shown to mitigate neurologic injury in some populations. In term and late preterm neonates with hypoxic ischemic encephalopathy, several studies have found reduced mortality and improved long-term neurodevelopmental outcomes when whole-body hypothermia was administered ≤6 hours after birth.[7-10] However, in other pediatric populations, including infants and children with cardiac arrest, the use of therapeutic hypothermia did not confer benefit on survival or neurologic outcomes.[11,12]

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The use of therapeutic hypothermia during ECMO as a neurologic protective strategy has gained interest among clinicians despite limited data.[13-16] Initial pilot studies in neonates treated with therapeutic hypothermia during ECMO did not report increased bleeding complications.[13,14] However, others have reported prolonged coagulation profiles, thrombocytopenia and bleeding events.[15] The Neonatal ECMO Study of Temperature (NEST) trial was a randomized trial to compare ECMO with therapeutic hypothermia versus standard ECMO in neonates requiring ECMO for reasons other than diaphragmatic hernia or post-cardiac surgery.[16] The use of hypothermia during ECMO did not result in improved outcomes at 2 years of age. Indeed, a pattern of small differences favoring standard ECMO was consistently observed across the health and neurologic outcomes investigated. In the current study, we use data from the multisite Bleeding and Thrombosis during ECMO (BATE) study[17] to further investigate the relationship between the use of therapeutic hypothermia during neonatal ECMO and complications, mortality and functional status among survivors.

Methods

Design and Setting

The study was a secondary analysis of data from the BATE study,[17] which investigated the incidence of bleeding and thrombosis in neonatal and pediatric ECMO patients. In the BATE study, observational data were collected prospectively at eight children's hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. The Institutional Review Boards for each hospital and the Data Coordinating Center at the University of Utah approved the study with waiver of parental permission.

Study Population

The BATE study included 514 neonatal and pediatric patients receiving ECMO in a neonatal, pediatric or cardiac intensive care unit (ICU).[17] In this secondary analysis, only neonatal patients (<30 days of age) were included (n=267). Only the initial ECMO course was included for patients who received ECMO more than once.

Data Collection

Data collected were gestational age at birth, age and weight at initiation of ECMO; primary diagnostic category (i.e., respiratory or non-respiratory); presence of meconium aspiration, congenital diaphragmatic hernia, or persistent pulmonary hypertension of the newborn; indication for ECMO; mode of ECMO; cardiopulmonary bypass (CPB) in 24 hours prior to ECMO; transition from CPB directly to ECMO; Oxygenation Index (OI),[18] Vasoactive Inotrope Score (VIS)[19,20] and presence of infection immediately prior to the initiation of ECMO; vital signs, blood laboratory values and volume of red cell transfusion during the first seven days of ECMO; clinical site; outcomes. Outcomes included complications during the first seven days of ECMO; duration of ECMO and ICU and hospital stay; survival to hospital discharge; functional status at hospital discharge among survivors.

Indications for ECMO were categorized as respiratory, cardiac or extracorporeal cardiopulmonary resuscitation (eCPR). The mode of ECMO was categorized as veno-arterial (VA) or veno-venous (VV). VV ECMO that was converted to VA was categorized as VA ECMO. The oxygenation index (OI) was calculated from the mean airway pressure (MAP), fraction of inspired oxygen (FiO_2) and partial pressure of oxygen in the arterial blood (PaO_2) as MAP x FiO_2 x 100/PaO_2.[18] The vasoactive inotrope score (VIS) was calculated from the hourly dose of dopamine, dobutamine, epinephrine, milrinone, vasopressin and norepinephrine.[19,20] Higher VIS scores indicate greater vasoactive and inotropic support. Infection was defined as a positive bacterial, fungal or viral culture or polymerase chain reaction (PCR) test. Vital signs and blood laboratory values were those collected closest to 7 am. Blood laboratory values included the platelet count, fibrinogen concentration, activated clotting time, arterial pH and lactate.

The use of therapeutic hypothermia was not recorded in the BATE study. For the purpose of this secondary analysis, we categorized patients as receiving therapeutic hypothermia if their core body temperature recorded closest to 7 am was ≤34°C for two consecutive days during the first three days of ECMO (i.e., Day 1 and 2 or Day 2 and 3). Therefore, the use of therapeutic hypothermia was based on two temperatures 24 hours apart. If the core body temperatures were not available, the blood temperature in the ECMO circuit was recorded. We defined therapeutic hypothermia in this manner because it is unlikely that patients receiving ECMO would have a core or blood temperature ≤34°C for this duration if it were not intentionally maintained.

Complications included neurologic events, bleeding events, thrombotic events, renal failure, hepatic dysfunction and new infection occurring on at least one day during the first seven days of ECMO. Neurologic events included seizures (clinical or electrographic), intracranial hemorrhage or infarction and brain death. Bleeding events were defined as blood loss with enough

clinical significance to require a transfusion or intracranial hemorrhage. Thrombotic events included intracranial infarction, limb ischemia, pulmonary embolus, intra-cardiac thrombus, aorto-pulmonary shunt thrombus, other sites of thrombosis and circuit thrombosis requiring replacement of a circuit component. Renal failure was defined as a creatinine concentration >176 μmol/L (>2 mg/dL) or use of renal replacement therapy. Hepatic dysfunction was defined as an International Normalized Ratio (INR) >2.

Functional status at hospital discharge was evaluated among survivors using the Functional Status Scale (FSS).[21] The FSS assesses function in 6 domains, including mental, sensory, communication, motor, feeding and respiratory. Domain scores range from 1 (normal) to 5 (very severe dysfunction). Total scores range from 6-30 and are categorized as 6-7 (good), 8-9 (mildly abnormal), 10-15 (moderately abnormal), 16-21 (severely abnormal) and >21 (very severely abnormal). Trained research coordinators collected FSS data via direct observation, discussion with bedside clinicians and review of medical records.

Statistical Analysis

Data were summarized using counts and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. The association between patient factors and therapeutic hypothermia use was evaluated with Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for ordinal variables. Reported p-values are based on a two-sided alternative. This approach was also used to establish the relationship between therapeutic hypothermia use and outcomes. The observed relationship between therapeutic hypothermia and intracranial hemorrhage was further investigated using multivariable Poisson regression models with robust error estimates based on generalized estimating equations. Importantly, the Poisson model considered the outcome of each ECMO day separately rather than as a single outcome for all study days. This approach provided greater power to detect associations and allowed assessment of covariates such as fibrinogen concentration that change from day to day. An autoregressive covariance structure of order 1 was specified to account for correlation between different study days on the same subject. In particular, this accounts for a higher correlation between study days that are close together, but relatively lower correlation between study days that are far apart. The process of building a multivariable model began with tests of univariable associations. Variables were considered potential predictors if they were associated with intracranial hemorrhage in univariable analysis ($p<0.10$) and available for at least 90% of the study days. The final model was selected using bi-directional stepwise selection on the potential predictors with a significance criterion of $p<0.10$ to enter and stay in the model. No variables were forced into the model. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Of 267 neonates undergoing ECMO, 20 received therapeutic hypothermia (Table 1). Neonates receiving therapeutic hypothermia were more likely to have a primary respiratory diagnosis and were more likely to have persistent pulmonary hypertension of the newborn than neonates not receiving therapeutic hypothermia. Neonates receiving therapeutic hypothermia were less likely to receive VA ECMO or to have received CPB in the 24 hours prior to the initiation of ECMO. No significant differences were observed in gestational age at birth or age or weight at initiation of ECMO between groups. Neonates undergoing ECMO received therapeutic hypothermia at seven of the eight participating sites.

Median body temperatures in the therapeutic hypothermia and non-hypothermia groups were 33.5°C (IQR 33.0, 33.7) vs 36.3°C (IQR 35.6, 36.7) on Day 1; 33.4°C (IQR 32.9, 33.6) vs 36.5°C (IQR 36.2, 36.8) on Day 2; and 33.5°C (IQR 33.3, 33.6) vs 36.6°C (IQR 36.3, 36.8) on Day 3. Body temperature over the first seven days of ECMO in the therapeutic hypothermia and non-hypothermia groups is shown in Figure 1.

Neonates receiving therapeutic hypothermia were more likely to develop an intracranial hemorrhage during the first seven days of ECMO than neonates not receiving therapeutic hypothermia (40.0% vs 15.8%, $p=0.012$) (Table 2). No significant difference was observed in hospital mortality, functional status at hospital discharge, duration of ECMO or duration of ICU or hospital stay between neonates receiving therapeutic hypothermia and neonates not receiving therapeutic hypothermia. Likewise, no significant difference was observed in the volume of red blood cells transfused or other complications during the first seven days of ECMO.

Univariable associations between patient factors and the development of intracranial hemorrhage during the first seven days of ECMO are displayed in the Supplementary Table S1. Using multivariable analysis, factors independently associated with intracranial hemorrhage in the first seven days of ECMO included the use of therapeutic hypothermia, gestational age at birth, age at initiation of ECMO, daily fibrinogen concentration and mode of ECMO (Table 3).

In total, 47 neonates developed intracranial hemorrhage during the first seven days of ECMO (Table 4). Neonates with intracranial hemorrhage had higher hos-

Table 1. Description of cohort by therapeutic hypothermia.

	Therapeutic hypothermia		p-value
	No (N = 247)	Yes (N = 20)	
Gestational age at birth (weeks)	38.0 [37.0, 39.0]	38.0 [38.0, 39.0]	0.947[1]
Age at ECMO initiation (days)	3.0 [1.0, 7.0]	1.0 [1.0, 3.0]	0.115[1]
Weight (kg)	3.1 [2.8, 3.5]	3.2 [2.7, 3.4]	0.837[1]
Male	156 (63.2%)	8 (40.0%)	0.055[2]
Primary ECMO indication			0.266[2]
Respiratory	136 (55.1%)	15 (75.0%)	
Cardiac	88 (35.6%)	4 (20.0%)	
eCPR	23 (9.3%)	1 (5.0%)	
Primary Diagnosis			0.020[2,3]
Respiratory			
Airway/tracheal	3 (1.2%)	0 (0.0%)	
Respiratory distress/failure	128 (51.8%)	16 (80.0%)	
Non-respiratory			
Cardiac arrest	4 (1.6%)	0 (0.0%)	
Cardiovascular disease - acquired	1 (0.4%)	0 (0.0%)	
Cardiovascular disease - arrhythmia	2 (0.8%)	0 (0.0%)	
Cardiovascular disease - congenital	105 (42.5%)	4 (20.0%)	
Congenital anomaly or chromosomal defect	1 (0.4%)	0 (0.0%)	
Hypoxic ischemic encephalopathy	1 (0.4%)	0 (0.0%)	
Sepsis/SIRS/septic shock	2 (0.8%)	0 (0.0%)	
Mode of ECMO			0.037[2]
VA	217 (87.9%)	14 (70.0%)	
VV	30 (12.1%)	6 (30.0%)	
CPB in the 24 hours prior to ECMO initiation	78 (31.6%)	2 (10.0%)	0.044[2]
Placed on ECMO directly from CPB	37 (15.0%)	1 (5.0%)	0.326[2]
Meconium aspiration syndrome	41 (16.6%)	6 (30.0%)	0.134[2]
Congenital diaphragmatic hernia	53 (21.5%)	3 (15.0%)	0.775[2]
Persistent pulmonary hypertension of the newborn	75 (30.4%)	13 (65.0%)	0.003[2]
Documented infection prior to ECMO initiation	11 (4.5%)	1 (5.0%)	1.000[2]
OI prior to ECMO initiation	29.4 [11.0, 50.2]	26.3 [16.0, 50.0]	0.817[1]
VIS prior to ECMO initiation			0.202[1]
None	62 (25.1%)	1 (5.0%)	
Low	77 (31.2%)	9 (45.0%)	
High	108 (43.7%)	10 (50.0%)	
Platelet count prior to ECMO initiation (10^9/L)	179.0 [132.5, 241.5]	163.0 [124.0, 231.0]	0.544[1]
Clinical Site			0.021[2]
A	39 (15.8%)	4 (20.0%)	
B	59 (23.9%)	3 (15.0%)	
C	21 (8.5%)	1 (5.0%)	
D	28 (11.3%)	0 (0.0%)	
E	18 (7.3%)	1 (5.0%)	
F	26 (10.5%)	8 (40.0%)	
G	16 (6.5%)	2 (10.0%)	
H	40 (16.2%)	1 (5.0%)	

ECMO: extracorporeal membrane oxygenation; eCPR: extracorporeal cardiopulmonary resuscitation; SIRS: systemic inflammatory response syndrome; VA: venoarterial; VV: venovenous; CPB: cardiopulmonary bypass; OI: oxygenation index; VIS: vasoactive inotrope score.
[1]the p-values for ordinal variables are based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range.
[2]the p-values for categorical variables are based on Fisher's exact test; for tables larger than 2x2, the p-value is estimated using Monte Carlo simulations. Data are expressed as counts and column percentages.
[3]The p-value for primary diagnosis is based on respiratory vs. non-respiratory and does not consider the subcategories.

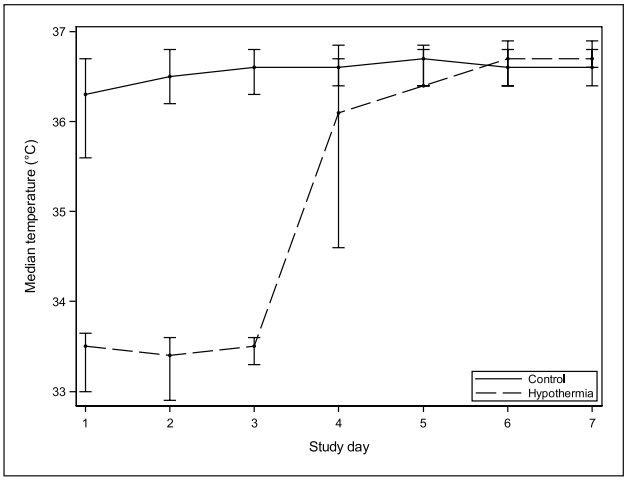

Figure 1. Body temperature during the first seven days of ECMO in the therapeutic hypothermia and non-hypothermia groups. Data represent the median and interquartile range.

pital morality than those without intracranial hemorrhage. Among survivors, neonates with intracranial hemorrhage tended to have worse functional status at hospital discharge than those without intracranial hemorrhage. Neonates with intracranial hemorrhage also had shorter duration of ICU and hospital stay.

Discussion

Our findings suggest that the use of therapeutic hypothermia during neonatal ECMO is independently associated with intracranial hemorrhage. Lower gestational age at birth, younger age at initiation of ECMO, use of VA ECMO and lower fibrinogen concentration during ECMO were also independently associated with intracranial hemorrhage. Despite an increased occurrence of intracranial hemorrhage in hypothermic neonates, no differences were observed between hypothermic and non-hypothermic neonates in hospital mortality or functional status at hospital discharge among survivors.

Early studies of therapeutic hypothermia during neonatal ECMO found hypothermia to be feasible and safe without coagulopathy or bleeding problems attributable to hypothermia.[13,14] A later case series by Massaro et al.[15] described five neonates with encephalopathy who met the inclusion criteria of the NICHD whole body hypothermia trial[7] and who were cooled to 33.5°C for 72 hours while receiving ECMO for meconium aspiration syndrome. All five neonates developed prolonged coagulation profiles and thrombocytopenia during therapeutic hypothermia. Massaro et al. report abnormalities in platelet count, fibrinogen, prothrombin time and partial thromboplastin time.[15] Three infants (60%) had intracranial hemorrhage: one with a small choroid plexus hemorrhage and two with subdural and intraparenchymal hemorrhage. Subsequently, the NEST trial randomized 111 neonates to ECMO with therapeutic hypothermia (34°C) or standard ECMO (37°C) for 48-72 hours from the start of their ECMO run.[16] Neonates received ECMO primarily for severe cardiorespiratory failure; those with diaphragmatic hernia or post-cardiac surgery were excluded. Although nearly all neonates (99%) had a head ultrasound performed prior to hospital discharge, the proportion in each group with intracranial hemorrhage of various degrees was not described. Among the serious adverse events reported, two neonates had large intracranial hemorrhage; both were in the ECMO with hypothermia group. In contrast, a recent retrospective study comparing ECMO with therapeutic hypothermia to standard ECMO in 96 children after cardiac surgery (median age 3.1 weeks) found that only two patients (2%) had intracranial bleeding; both in the standard ECMO group.[22]

These inconsistent findings regarding the risk of intracranial hemorrhage in neonates treated with therapeutic hypothermia during ECMO may be due, in part, to differences in the populations studied and study designs. For example, neonates receiving ECMO for respiratory diagnoses may experience prolonged periods of hypoxia and hypercarbia in the pre-ECMO phase of illness that can disrupt cerebral autoregulation and increase the brain's vulnerability to hyperemia and hemorrhage during the ECMO course.[23,24] In our study, 80% of neonates treated with therapeutic hypothermia during ECMO had a primary respiratory diagnosis and 65% had persistent pulmonary hypertension. In a recent study of neonates treated with standard ECMO for persistent pulmonary hypertension, 34% developed intracranial hemorrhage.[25] This rate is higher than the 7.5-11.2% rate of intracranial hemorrhage reported for neonatal ECMO in the Extracorporeal Life Support Organization (ELSO) Registry.[26] The high proportion of neonates undergoing ECMO with primary respiratory diagnoses and persistent pulmonary hypertension in our therapeutic hypothermia group could potentially have contributed to their risk for intracranial hemorrhage. However, in our study, neither having a primary respiratory diagnosis nor persistent pulmonary hypertension was associated with intracranial hemorrhage (Supplementary Table S1).

Hypothermia may cause platelet dysfunction, a mild decrease in platelet count and alterations in the coagulation cascade.[27,28] In addition, hypothermia and rewarming have been associated with fluctuation in cerebral blood flow.[29,30] These factors in combination with the prolonged coagulation profile and decreased platelet count typical of neonates undergoing ECMO may partly explain the association between therapeutic hypothermia and intracranial hemorrhage in this population.[31-33]

Our findings suggest that lower gestational age at birth and younger age at initiation of ECMO are inde-

Table 2. Complications and outcomes by therapeutic hypothermia.

	Therapeutic hypothermia		p-value
	No (N = 247)	Yes (N = 20)	
In-hospital mortality	107 (43.3%)	6 (30.0%)	0.347[1]
Functional status at hospital discharge			0.380[2]
Good	46 (18.6%)	5 (25.0%)	
Mildly abnormal	62 (25.1%)	8 (40.0%)	
Moderately abnormal	27 (10.9%)	1 (5.0%)	
Severely abnormal	5 (2.0%)	0 (0.0%)	
Not applicable (dead)	107 (43.3%)	6 (30.0%)	
Duration of ECMO (days)	5.3 [2.8, 10.1]	6.7 [3.9, 9.1]	0.742[2]
Duration of ICU stay (days)	29.0 [15.3, 53.0]	30.0 [14.8, 53.0]	0.941[2]
Duration of hospital stay (days)	33.6 [16.4, 59.2]	40.5 [15.0, 65.8]	0.901[2]
Complications in the first seven days of ECMO			
New documented infection	19 (7.7%)	0 (0.0%)	0.376[1]
Bleeding event	144 (58.3%)	15 (75.0%)	0.163[1]
Thrombotic event	70 (28.3%)	5 (25.0%)	1.000[1]
Intracranial hemorrhage	39 (15.8%)	8 (40.0%)	0.012[1]
Neurologic event	82 (33.2%)	9 (45.0%)	0.329[1]
Renal failure	74 (30.0%)	9 (45.0%)	0.208[1]
Hepatic failure	78 (31.6%)	6 (30.0%)	1.000[1]
Mean daily RBC transfusion in first seven days of ECMO (mL/kg)	35.8 [27.3, 55.9]	45.0 [27.7, 70.4]	0.628[2]

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RBC: red blood cell.
[1]the p-values for categorical variables are based on Fisher's exact test. Data are expressed as counts and column percentages.
[2]the p-values for ordinal variables are based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range or as counts and column percentages.

Table 3. Multivariable model for intracranial hemorrhage.

Variable	Adjusted Relative Risk (95% CI)	p-value
Age at ECMO initiation (days)	0.90 (0.84, 0.97)	0.007
Gestational age at birth (weeks)	0.81 (0.70, 0.94)	0.004
Therapeutic hypothermia	2.98 (1.12, 7.94)	0.029
Daily fibrinogen concentration (0.29 µmol/L (10 mg/dL))	0.95 (0.92, 0.98)	<0.001
Mode of ECMO		0.036
VA	Reference	
VV	0.24 (0.07, 0.91)	

ECMO: extracorporeal membrane oxygenation; VA: venoarterial; VV: venovenous.
Wald confidence intervals and p-values for the adjusted relative risk are based on the Poisson regression model with the autoregressive covariance structure of order 1 within subjects and robust error estimates.

pendently associated with intracranial hemorrhage. Others have similarly reported that gestational age at birth, postnatal age and post-conceptual age are related to the risk of intracranial hemorrhage during ECMO.[34-36] Using the ELSO registry to investigate the frequency of intracranial hemorrhage and mortality among neonates receiving ECMO for respiratory failure, Smith et al.[36] found both gestational age and postnatal age to influence these outcomes. Older neonates (>7 days postnatal age) had less intracranial hemorrhage, but greater mortality compared to younger neonates (<7 days). Prematurity was associated with intracranial hemorrhage only among neonates <7 days of age. Differences in respiratory diagnoses and pathophysiologic processes between older and younger neonates were suggested explanations for the differences in outcomes observed. For example, younger neonates were more likely to have meconium aspiration as the indica-

Table 4. Association between intracranial hemorrhage in the first seven days of ECMO and outcomes.

	Intracranial hemorrhage in the first 7 days of ECMO		p-value
	No (N = 220)	Yes (N = 47)	
In-hospital mortality	84 (38.2%)	29 (61.7%)	0.004[1]
Functional status at hospital discharge (among survivors)			0.060[2]
Good	48 (35.3%)	3 (16.7%)	
Mildly abnormal	61 (44.9%)	9 (50.0%)	
Moderately abnormal	22 (16.2%)	6 (33.3%)	
Severely abnormal	5 (3.7%)	0 (0.0%)	
Duration of ECMO (days)	5.3 [2.8, 9.9]	5.0 [2.8, 11.3]	0.990[2]
Duration of hospital stay (days)	35.7 [18.7, 62.9]	22.2 [6.9, 50.0]	0.007[2]
Duration of ICU stay (days)	30.3 [16.1, 54.0]	20.1 [6.8, 48.9]	0.046[2]

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.
[1]Fisher's exact test. Data are expressed as counts and column percentages.
[2]P-value is based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range.

tion for ECMO than were older neonates and meconium aspiration had a lower risk of mortality than other diagnoses in both age groups. Germinal matrix maturation over the first few days of life in premature infants may partly explain why prematurity was associated with intracranial hemorrhage only in infants <7 days of age.

The use of VA ECMO compared to VV ECMO was independently associated with intracranial hemorrhage in our study population. Others have also described the increased risk of intracranial hemorrhage with VA ECMO;[36,37] however, comparisons between ECMO modes are also confounded by differences in patient populations since VA ECMO rather than VV is typically used for cardiac support. Some have suggested that loss of pulsatile arterial flow during VA ECMO disturbs cerebral autoregulation and contributes to the increased risk of intracranial hemorrhage.[24] Lower daily fibrinogen concentration was also independently associated with intracranial hemorrhage in our study population. Previous studies both confirm and refute this finding.[25,38] Contrary to earlier reports, we did not find an association between platelet count or activated clotting time and intracranial hemorrhage.[25,39,40] Many interrelated components contribute to coagulation during ECMO and monitoring and treatment of any single component is likely to be insufficient to prevent intracranial hemorrhage.

Strengths of this study include the multisite design and daily prospective collection of data from all neonates treated with ECMO during the study period. Strengths of the analysis include considering the occurrence of intracranial hemorrhage on each study day separately rather than as a single outcome for all study days. This method allowed covariates that changed from day to day (e.g., fibrinogen) and the time course of events to be taken into consideration. For example, average fibrinogen concentration versus intracranial hemorrhage on any study day up to day 7 does not incorporate the timing of the hemorrhage relative to the changing fibrinogen levels. Considering daily outcomes increases the power to detect relationships and the relationships detected are more meaningful than would otherwise be possible.

Limitations of this study include the lack of prospective documentation of the use of therapeutic hypothermia during ECMO and, hence, the need to define the therapeutic hypothermia group retrospectively. We categorized patients as receiving therapeutic hypothermia if their core body temperature recorded closest to 7 am was ≤34°C for two consecutive days during the first three days of ECMO (i.e., Day 1 and 2 or Day 2 and 3). Therefore, the use of therapeutic hypothermia was based on two temperatures 24 hours apart; oscillations in temperature during this period are not accounted for, which is a major limitation of the study and may have affected our results. Indications for therapeutic hypothermia and details of management (e.g., method of cooling, intended depth and duration of cooling) were not collected. Only twenty neonates receiving therapeutic hypothermia during ECMO were identified during the study period.

The design of our study as a secondary analysis also poses limitations; for example, some important data elements were not collected in the original BATE dataset, such as baseline head ultrasound results prior to cannulation. The lack of baseline head ultrasound is a major limitation of our study. While many of our patients probably had pre-ECMO head ultrasounds, these reports were not collected in the BATE study. Therefore, it is possible that a pre-existing intracranial hemorrhage was classified as new. Head ultrasound was performed

during ECMO at the discretion of the clinicians and the frequency of head ultrasound during ECMO was not standardized. Therefore, increased surveillance with head ultrasound could, potentially, explain the increased frequency of intracranial hemorrhage in the hypothermia group. Additionally, reports describing the intracranial hemorrhages in terms of location and size were not collected. Other practices, such as anticoagulation and transfusion practices, were also not standardized.

Conclusions

An increased occurrence of intracranial hemorrhage among neonates treated with therapeutic hypothermia during ECMO was observed in this study. Although therapeutic hypothermia mitigates neurologic injury in some populations, the increased occurrence of intracranial hemorrhage observed when therapeutic hypothermia is applied during neonatal ECMO should serve as a caution to clinicians about the potential risks of applying research findings from one patient population to another without sufficient evidence. The use of therapeutic hypothermia during neonatal ECMO merits further study.

Acknowledgements

The authors wish to acknowledge the contributions of the following CPCCRN principal investigators, research coordinators and data coordinating center staff: Stephanie Bisping, BSN, RN, CCRP, Alecia Peterson, BS and Jeri Burr, MS, RN-BC, CCRC from University of Utah; Robert A. Berg, MD, Mary Ann DiLiberto, BS, RN, CCRC and Carol Ann Twelves, BS, RN from The Children's Hospital of Philadelphia; David Wessel, MD, Jean Reardon, MA, BSN, RN and Elyse Tomanio, BSN, RN from Children's National Medical Center; Murray M. Pollack, MD and Aimee Labell, MS, RN from Phoenix Children's Hospital; Christopher J. L. Newth, MD, Margaret Villa, RN and Jeni Kwok, JD from Children's Hospital Los Angeles; Rick Harrison, MD and Mary Ann Nyc, BS from UCLA Mattel Children's Hospital; Ann Pawluszka, BSN, RN and Melanie Lulic, BS from Children's Hospital of Michigan; Thomas P. Shanley, MD, Monica S. Weber, RN, BSN, CCRP and Lauren Conlin, BSN, RN, CCRP from University of Michigan; Joseph Carcillo, MD and Alan C. Abraham, BA, CCRC from University of Pittsburgh Medical Center; and Robert Tamburro, MD and Tammara Jenkins, MSN, RN from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the following cooperative agreements from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services: U10HD050096, U10HD049981, U10HD049983, U10HD050012, U10HD063108, U10HD063106, U10HD063114, and U01HD049934. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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References

1. UK Collaborative ECMO Trial Group. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996; 348: 75–82.
2. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. *Cochrane Database of Syst Rev* 2008; 16: CD001340.
3. McNally H, Bennett CC, Elbourne D, et al. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. *Pediatrics* 2006; 117: e845-e854.
4. Madderom MJ, Reuser JJ, Utens EM, et al. Neurodevelopmental, educational and behavioral outcome at 8 years after neonatal ECMO: a nationwide multicenter study. *Intensive Care Med* 2013; 39: 1584–1593.
5. von Bahr V, Hultman J, Eksborg S, et al. Long-term survival and causes of late death in children treated with extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2017; 18: 272–280.
6. Cashen K, Reeder R, Dalton H, et al. Functional status of neonatal and pediatric patients after extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2017: 18: 561–570.
7. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; 353: 1574–1584.
8. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; 361: 1349–1358.
9. Simbruner G, Mittal RA, Rohlmann F, et al. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics* 2010; 126: e771-e778.
10. Jacobs SE, Morley CJ, Inder TE, et al. Whole-body hypothermia for term and near-term newborns with hypoxic ischemic encephalopathy: a randomized controlled trial. *Arch Pediatr Adolesc Med* 2011; 165: 692–700.
11. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med* 2015; 372: 1898–1908.
12. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med* 2017; 376: 318–329.
13. Horan M, Ichiba S, Firmin RK, et al. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). *J Pediatr* 2004; 144: 301–308.

14. Ichiba S, Killer HM, Firmin RK, et al. Pilot investigation of hypothermia in neonates receiving extracorporeal membrane oxygenation. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F128–133.
15. Massaro A, Rais-Bahrami K, Chang T, et al. Therapeutic hypothermia for neonatal encephalopathy and extracorporeal membrane oxygenation. *J Pediatr* 2010; 157: 499–501.
16. Field D, Juszczak E, Linsell L, et al. NEST Study Collaborative Group. Neonatal ECMO study of temperature (NEST); a randomized controlled trial. *Pediatrics* 2013; 132: e1247-e1256.
17. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation (ECMO). *Am J Respir Crit Care Med* 2017; 196: 762–771.
18. Ortiz RM, Cilley RE, Bartlett RH. Extracorporeal membrane oxygenation in pediatric respiratory failure. *Pediatr Clin North Am* 1987; 34: 39–46.
19. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010; 11: 234–238.
20. Gaies MG, Jeffries HE, Niebler RA, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. *Pediatr Crit Care Med* 2014; 15: 529–537.
21. Pollack MM, Holubkov R, Glass P, et al. Functional Status Scale: new pediatric outcome measure. *Pediatrics* 2009; 124: e18–e28.
22. Lou S, MacLaren G, Paul E, et al. Safety of therapeutic hypothermia in children on veno-arterial extracorporeal membrane oxygenation after cardiac surgery. *Cardiol Young* 2015; 25: 1367–1373.
23. Short BL. The effect of extracorporeal life support on the brain: a focus on EMCO. *Semin Perinatol* 2005; 29: 45–50.
24. De Mol AC, Liem KD, van Heijst AFJ. Cerebral aspects of neonatal extracorporeal membrane oxygenation: a review. *Neonatology* 2013; 104: 95–103.
25. Doymaz S, Zinger M, Sweberg T. Risk factors associated with intracranial hemorrhage in neonates with persistent pulmonary hypertension on ECMO. *J Intensive Care* 2015; 3: 6.
26. ELSO. Registry of the extracorporeal life support organization. Ann Arbor, MI: ELSO; www.elsonet.org. (2017, accessed 4 April 2017).
27. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 2009; 37: 1101–1120.
28. Jacobs S, Hunt R, Tarnow-Mordi W, et al. Cooling for newborns with hypoxic ischemic encephalopathy. *Cochrane Database Syst Rev* 2007: CD00331129.
29. Massaro AN, Bouyssi-Kobar M, Chang T, et al. Brain perfusion in encephalopathic newborns after therapeutic hypothermia. *AJNR Am J Neuroradiol*. 2013; 34: 1649–1655.
30. Wintermark P, Hansen A, Gregas MC, et al. Brain perfusion in asphyxiated newborns treated with therapeutic hypothermia. *AJNR Am J Neuroradiol*. 2011; 32: 2023–2029.
31. Al Yazidi G, Boudes E, Tan X, et al. Intraventricular hemorrhage in asphyxiated newborns treated with hypothermia: a look into incidence, timing and risk factors. *BMC Pediatrics* 2015; 15: 106.
32. Plotz FB, van Oeveren W, Bartlett RH, et al. Blood activation during neonatal extracorporeal life support. *J Thorac Cardiovasc Surg* 1993; 105: 823–832.
33. Robinson TM, Kickler TS, Walker LK, et al. Effect of extracorporeal membrane oxygenation on platelets in newborns. *Crit Care Med* 1993; 21: 1029–1034.
34. Hardart GE, Fackler JC. Predictors of intracranial hemorrhage during neonatal extracorporeal membrane oxygenation. *J Perinatol* 1999; 134: 156–159.
35. Hardart GE, Hardart KM, Arnold JH. Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptional age. *J Pediatr* 2004; 145: 184–189.
36. Smith KM, McMullan DM, Bratton SL, et al. Is age at initiation of extracorporeal life support associated with mortality and intraventricular hemorrhage in neonates with respiratory failure? *J Perinatol* 2014; 34: 386–391.
37. Varnholt V, Lasch P, Sartoris J, et al. Prognosis and outcome of neonates treated either with venoarterial (va) or veno-venous (vv) ECMO. *Int J Artif Organs* 1995; 18: 569–573.
38. Anton-Martin P, Journeycake J, Modem V, et al. Coagulation profile is not a predictor of acute cerebrovascular events in pediatric extracorporeal membrane oxygenation patients. *ASAIO J* 2017; doi: 10.1097/MAT.0000000000000571. [Epub ahead of print.]
39. Dela Cruz TV, Stewart DL, Winston SJ, et al. Risk factors for intracranial hemorrhage in the extracorporeal membrane oxygenation patient. *J Perinatol* 1997; 17: 18–23.
40. Hirthler MA, Blackwell E, Abbe D, et al. Coagulation parameter instability as an early predictor of intracranial hemorrhage during extracorporeal membrane oxygenation. *J Pediatr Surg* 1992; 27: 40–43.