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Original Article

Patterns of Head Computed Tomography Abnormalities During Pediatric Extracorporeal Membrane Oxygenation and Association With Outcomes

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ABSTRACT

BACKGROUND: We sought to classify type and distribution of acute infarction and hemorrhage on head computed tomography (CT) during pediatric extracorporeal membrane oxygenation (ECMO). We also analyzed the occurrence of seizures on electroencephalography and outcomes between those with and without CT abnormalities. **METHODS:** We conducted a single center observational study in pediatric intensive care units. The medical records of 179 children who underwent ECMO between 2009 and 2013 were reviewed. No interventions were done. **RESULTS:** A total of 46% (82/179) of children underwent CT. Of these, 60% (49/82) had acute pathology. Cerebral infarction occurred in 55% (27/49) and hemorrhage in 41% (20/49). Infarction was arterial in 67% (18/27) with a preponderance in the middle cerebral artery territory (17 patients). Infarction was bilateral in 41% (11/27) and not specific to the side of cannulation in the rest. Sensitivity and specificity for head ultrasound in predicting infarction on CT were 100% and 53%, respectively. A total of 36% (65/179) underwent continuous encephalography monitoring; 22% (14/65) of these had electrographic seizures. Electrographic seizures were increased in those with infarction (odds ratio [OR], 6.81; 95% confidence interval [CI], 1.98 to 23.43). Survival was reduced with both infarction (OR, 0.22; 95% CI, 0.09 to 0.54) and hemorrhage (OR, 0.31; 95% CI, 0.13 to 0.72). Children with CT abnormalities had more unfavorable outcomes ($P = 0.01$). **CONCLUSIONS:** Head ultrasound is insufficient to rule out infarction. Infarction is middle cerebral artery predominant and associated with an increased risk of electrographic seizures.

Keywords: extracorporeal membrane oxygenation, x-ray computed tomography, cerebral infarction, cerebral hemorrhage, electroencephalography

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Introduction

Neonates and children who develop cerebral hemorrhage and infarction during cardiopulmonary life support with extracorporeal membrane oxygenation (ECMO) have reduced survival rates and increased risk of long-term neurodevelopmental disabilities in survivors compared with those without these abnormalities.[1-7] Risk factors for ischemic stroke in ECMO patients appear to differ from those for hemorrhagic stroke. For ischemic stroke, risk factors

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include age less than 30 days and a respiratory indication for ECMO.[1] For intracranial hemorrhage, risk factors are age less than 30 days, sepsis, cardiopulmonary resuscitation before or during ECMO, and a cardiac indication for ECMO.[1,4,8,9] Systematic classification of patterns of infarction and hemorrhage detected on head imaging during the course of ECMO in children is lacking. An improved understanding of these patterns is needed to better understand risk factors and mechanisms that may be contributing to a particular type of cerebral insult and assess outcomes.

The reported incidence of imaging abnormalities in ECMO recipients varies, with higher rates reported when cranial computed tomography (CT) is performed.[10,11] In this single-center retrospective study, we sought to describe the type and distribution of abnormalities detected on head CT during the course of ECMO in children. We also compared clinical factors, including the occurrence of seizures detected on electroencephalography (EEG) and outcomes, between those with CT abnormalities and those without imaging abnormalities.

Methods

The Institutional Review Board granted ethical approval with a waiver for study of retrospective, electronic data.

Patient population and data collection

The medical records of 179 patients who were treated with venoarterial (VA) and venovenous (VV) ECMO in the intensive care units at Boston Children's Hospital between the years 2009 and 2013 were reviewed.

Data extracted from the medical records included age, gender, indication for ECMO, and mortality. Indications for ECMO were categorized as cardiac or respiratory, after cardiopulmonary bypass in the operating room (OR-ECMO), and to aid cardiopulmonary resuscitation (E-CPR). Type of ECMO (VA or VV), ECMO duration, and arterial cannula location were recorded. Maximum and minimum partial thromboplastin time values, activated clotting time, and anti-Xa values were recorded during the course of ECMO. Peak serum lactate values at the time of cannulation and up to the first CT scan were recorded. A pragmatic approach was taken to group patients by "ischemia risk" at the time of cannulation using clinical variables that are recognizable as being severe at the time of cannulation. Ischemia risk was calculated for the entire cohort and defined as having an inotrope score $\geq$20, serum lactate $\geq$3.9 mmol/L, and requirement for E-CPR. The inotrope score has been validated as a measure of cardiovascular support.[12] The lactate concentration level $\geq$3.9 mmol/L was chosen because this is the threshold for critically high in our laboratory.

Recordings of all EEG studies obtained during the course of ECMO were reviewed (C.H., pediatric epileptologist). Timing of EEG from cannulation and total hours of recording time were noted. Electrographic seizures were recorded if they occurred at any point during the recording. Seizure activity was defined by ten seconds of any rhythmic electrical pattern, or shorter if associated with clinical change.[13,14] Clinical signs noted on video review were recorded if they were associated with an electrographic seizure. Suppression was noted if the entirety of the EEG record consisted of activity less than 10 μV in longitudinal bipolar montage with standard 10-20 electrodes (measured from peak to trough).

Images from the first abnormal head CT study obtained during ECMO were reviewed by a neuroradiologist (S.P.P.) who was unawareof all clinical information. Head CT studies were assessed for the presence of extra-axial hemorrhage, intraventricular hemorrhage, intraparenchymal hemorrhage (IPH), infarction, cerebral venous sinus thrombosis, and diffuse edema. For each patient with cerebral infarction, distribution of parenchymal involvement on the first abnormal head CT was classified. For arterial infarction, the arterial distributions involved were recorded as middle cerebral artery (MCA), anterior cerebral artery, and posterior cerebral artery. Arterial infarction was defined as focal if only one arterial territory was involved, and multifocal if two or more arterial distributions were affected. Laterality of arterial distribution involved was noted (bilateral, right, or left).

Final reports of all head ultrasounds obtained during the course of ECMO were reviewed. A head ultrasound study was scored as abnormal if any report indicated the presence of hemorrhage, increased echogenicity, or edema, suggestive of infarction or hemorrhage.

Neurological surveillance on ECMO

A neurological consultation was obtained for all patients on ECMO. Most patients treated with ECMO receive continuous infusions of midazolam, morphine, and cisatracurium. Pharmacologic paralysis is lifted for neurological examinations at the discretion of the primary care team. All subjects in this study met institutional criteria for ECMO. Anticoagulation, hematocrit, platelet, and oxygenation goals were maintained according to the institutional protocol. Portable head ultrasound is used to screen for acute abnormalities before cannulation, if possible; within 24 hours after cannulation; and every 48 hours thereafter. The decision to pursue further neurodiagnostic studies (e.g., CT and EEG) is made collaboratively among a multidisciplinary team.

All head CT studies were performed when clinically indicated. Clinical indications for CT imaging included follow up of an abnormal head ultrasound, pupillary changes or other new focal neurological deficit, papilledema, bulging fontanel, seizure, delayed awakening from sedation, cardiac arrest, or changes in vital signs suspicious for raised intracranial pressure (e.g., hypertension or bradycardia). The head CT device used is a commercially available, Food and Drug Administration-approved portable scanner (CereTom; Neurologica, Danvers, MA).[15] EEG monitoring was performed continuously using a conventional video-electroencephalographic system (Natus Medical, Madison, WI). The duration of continuous EEG monitoring is at the discretion of the primary clinical service. Clinical indications for EEG monitoring included clinical signs observed by bedside caregivers suspicious for seizure (e.g., abnormal extremity movements or pupillary changes), paroxysmal changes in vital signs (e.g., tachycardia and hypertension), delayed awakening, or cardiac arrest.

Outcomes

The primary outcome was the development of cerebral infarction or hemorrhage on head CT during ECMO. Secondary outcomes were mortality and functional outcome at hospital discharge. Functional outcome was scored using the Pediatric Cerebral Performance Category Scale (PCPC), which is a validated 6-point scale (1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma and vegetative state, and 6 = death).[16] Favorable outcome was defined as PCPC scores of 1 to 2, and unfavorable outcome was defined as PCPC scores of 3 to 6.

Data analysis

For descriptive statistics, chi-square or Fisher's exact test (in case of cell count less than five) was used to summarize categorical variables. Mean and S.D. were used to summarize continuous normal data. Skewed continuous measures were summarized with median and interquartile range (IQR). Bivariate analysis was used to assess the association among gender, primary diagnosis of congenital heart disease, electrographic seizure, survival rate, ischemia risk, PCPC scores, and radiographic outcome of cerebral infarction or intracranial hemorrhage. Serum lactate as a predictor of abnormal head CT imaging was analyzed by receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC-ROC) of the best-fitting model was used as an indicator of its predictive ability. P values <0.05 were considered statistically significant. All analyses were performed using statistical analysis system (SAS) version 9.4 software (SAS Institute Inc, SAS statistical software, Cary, NC).

Results

A total of 46% (82/179) of children underwent 113 portable CT scans. Of these, 60% (49/82) had cerebral