One-Year Survival and Neurologic Outcomes After Pediatric Open-Chest Cardiopulmonary Resuscitation

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Background. **Limited data exist about neurobehavioral outcomes of children treated with open-chest cardiopulmonary resuscitation (CPR). Our objective was to describe neurobehavioral outcomes 1 year after arrest among children who received open-chest CPR during in-hospital cardiac arrest and to explore factors associated with 1-year survival and survival with good neurobehavioral outcome.**

Methods. **The study is a secondary analysis of the Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital Trial. Fifty-six children who received open-chest CPR for in-hospital cardiac arrest were included. Neurobehavioral status was assessed using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at baseline before arrest and 12 months after arrest. Norms for VABS-II are 100 ± 15 points. Outcomes included 12-month survival, 12-month survival with VABS-II decreased by no more than 15 points from baseline, and 12-month survival with VABS-II of 70 or more points.**

Results. **Of 56 children receiving open-chest CPR, 49 (88%) were after cardiac surgery and 43 (77%) were younger than 1 year. Forty-four children (79%) were cannulated for extracorporeal membrane oxygenation (ECMO) during CPR or within 6 hours of return of spontaneous circulation. Thirty-three children (59%) survived to 12 months, 22 (41%) survived to 12 months with VABS-II decreased by no more than 15 points from baseline, and of the children with baseline VABS-II of 70 or more points 23 (51%) survived to 12 months with VABS-II of 70 or more points. On multivariable analyses, use of ECMO, renal replacement therapy, and higher maximum international normalized ratio were independently associated with lower 12-month survival with VABS-II of 70 or more points.**

Conclusions. **Approximately one-half of children survived with good neurobehavioral outcome 1 year after open-chest CPR for in-hospital cardiac arrest. Use of ECMO and postarrest renal or hepatic dysfunction may be associated with worse neurobehavioral outcomes.**

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The Society of Thoracic Surgeons Task Force on Resuscitation after Cardiac Surgery recommends early emergency resternotomy for children and adults who arrest after cardiac surgery and fail to achieve return of spontaneous circulation after immediate correction of readily reversible causes [1]. Specifically, The Society of Thoracic Surgeons recommend resternotomy within 5 minutes for ventricular fibrillation or pulseless ventricular tachycardia unresponsive to three sequential defibrillation attempts, asystole, or severe bradycardia unresponsive to pacing and pulseless electrical activity without a quickly reversible cause. Emergency resternotomy allows for the treatment of tamponade or hypovolemia caused by intrathoracic bleeding, both common causes of arrest after cardiac surgery. Emergency resternotomy also allows for the provision of direct cardiac compressions through the open chest. Animal studies suggest that open-chest cardiac

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compressions result in greater cardiac index and coronary perfusion pressure than closed-chest compressions, although human data are sparse [2]. In addition, use of open-chest cardiac compressions can potentially prevent complications observed with closed-chest compressions such as rupture of cardiac chambers, prosthetic valve dehiscence, and vascular dissection [3]. Open-chest cardiopulmonary resuscitation (CPR) has also been used for traumatic cardiac arrest; however, recent studies found no significant improvement in outcomes compared with closed-chest CPR in the setting of blunt or penetrating trauma [4, 5].

Limited data exist about long-term survival and neurologic outcomes of patients, especially children, treated with open-chest CPR. The Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial was a randomized trial that compared the efficacy of therapeutic hypothermia with that of therapeutic normothermia on survival with good neurobehavioral outcome in children 1 year after in-hospital cardiac arrest [6]. Although no significant benefit on survival with good neurobehavioral outcome was observed with either temperature management intervention, the THAPCA-IH database can be used to explore outcomes of children exposed to other aspects of resuscitation or care after arrest. Children recruited to the THAPCA-IH trial were comatose after arrest and at high risk of neurologic disability. Neurobehavioral function was evaluated in the THAPCA-IH trial by using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at baseline (reflecting status before arrest) and 1 year after arrest [7]. The objective of this study was to describe neurobehavioral outcomes 1 year after arrest among children who received open-chest CPR and were recruited to the THAPCA-IH trial and to explore factors associated with 1-year survival and survival with good neurobehavioral outcome.

Patients and Methods

Design and Setting

This study is a secondary analysis of the THAPCA-IH trial [6]. Thirty-seven children's hospitals in the United States, Canada, and the United Kingdom recruited children between September 1, 2009, and February 27, 2015. Details of the THAPCA-IH trial were previously published [6, 8]. Institutional review boards at each study site, the Kennedy Krieger Institute Outcome Assessment Center, and the University of Utah Data Coordinating Center approved the study. Caregiver permission was obtained for all participants.

Participants

Inclusion criteria for the THAPCA-IH trial were age older than 48 hours and younger than 18 years, occurrence of an in-hospital cardiac arrest with chest compressions for 2 or more minutes, need for mechanical ventilation after return of circulation, and a Glasgow Coma Scale motor score less than 5 [9]. A Glasgow Coma Scale motor score of 5 represents localizing pain or (if younger than 2 years) withdrawing to touch. Additional inclusion criteria for this secondary analysis included receipt of open-chest CPR. Exclusion criteria for the THAPCA-IH trial included inability to be randomized within 6 hours of return of circulation, cardiac arrest due to trauma, and a decision to withhold aggressive treatment. A full list of exclusion criteria was previously published [6, 8]. Of 329 children randomly assigned in the THAPCA-IH trial, 56 received open-chest CPR.

Independent Variables

Trained research coordinators collected data at the time of study entry by medical record review and direct interaction with caregivers and clinicians. Child characteristics included age, sex, body habitus, technology dependence, being postoperative from cardiac surgery at the time of arrest, previous intensive care unit (ICU) admissions during the hospitalization, and preexisting conditions. Body habitus was evaluated by using body mass index-for-age percentiles for children 2 years or older and weight-for-length percentiles for children younger than 2 years [10]. Children were considered obese if their body mass index-for-age or weight-for-length was greater than the 95th percentile and underweight if less than the fifth percentile as recommended by the US Centers for Disease Control and Prevention [10]. Technology dependence was defined as presence of a tracheostomy or percutaneous feeding tube before the cardiac arrest. Children categorized as postoperative cardiac surgery had a cardiac surgical procedure during the hospitalization in which the arrest occurred. Preexisting conditions included cardiac, respiratory, neurologic, gastrointestinal, prenatal, pulmonary hypertension, renal, and other conditions. Preexisting cardiac conditions were categorized as single ventricle or not.

Cardiac arrest characteristics included primary cause of arrest, initial cardiac rhythm at the time chest compressions were started, duration of chest compressions, number of epinephrine doses administered during the arrest, epinephrine-dosing interval, whether cardiac defibrillation was attempted, location of arrest within the hospital, and presence of an intravenous catheter or endotracheal tube at the time of arrest. Primary cause of arrest was categorized as cardiovascular or respiratory. Initial cardiac rhythm was categorized as asystole, bradycardia, pulseless electrical activity, ventricular tachycardia/fibrillation, or unknown. Epinephrine-dosing interval was defined as the duration of chest compressions divided by the total number of epinephrine doses administered during chest compressions. Location of arrest was categorized as ICU (including intermediate care), operating room, non-ICU inpatient ward, or other clinical area.

Postarrest characteristics included the THAPCA-IH trial intervention (ie, therapeutic hypothermia versus therapeutic normothermia) and use of extracorporeal membrane oxygenation (ECMO) at the time of initiation of the temperature management intervention (ie, ECMO cannulation either during CPR or within 6 hours of return of spontaneous circulation). Postarrest characteristics also included the presence of clinical or electrographic seizures and the use of renal replacement therapy from the time of randomization in the THAPCA-IH trial through day 5 of the trial, and the presence of serious arrhythmias, culture-positive infection, and the use of blood products from the time of randomization through day 7. Laboratory data included postarrest arterial blood pH and lactate, international normalized ratio (INR), total bilirubin, and alanine aminotransferase. The minimum and maximum values for each of these in the time interval from 2 hours before to 48 hours after the start of the temperature management intervention were recorded.

Outcomes

Outcomes included 12-month survival, 12-month survival with VABS-II decreased by no more than 15 points from baseline, and 12-month survival with VABS-II of 70 or more points [7]. The VABS-II is a caregiver report measure of adaptive behavior from birth to adulthood. Adaptive behavior is defined as performance on daily life activities necessary for personal and social independence. VABS-II domains include communication, daily living, socialization, and motor skills. The number of tasks that can be performed in each domain is standardized for the child's age. In normative US populations, the mean VABS-II is 100 points, and the standard deviation is 15 points. Higher scores indicate better functioning. Caregivers completed baseline VABS-II assessments (reflecting prearrest status) at the local sites within 24 hours of randomization into the THAPCA-IH trial and 12-month assessments by telephone with interviewers from the Kennedy Krieger Institute who were blinded to treatment group assignment. For the outcome of survival with VABS-II of 70 or more points, only children with baseline VABS-II of 70 or more points ($n = 47$) were considered.

Statistical Analysis

Cardiac arrest and postarrest characteristics were summarized using frequencies and percentages. Univariate associations between these characteristics and the outcomes were examined with Fisher's exact test or the Cochran-Armitage exact test for trend. Laboratory values were summarized as medians and quartiles. Univariate associations between laboratory values and outcomes were examined with Wilcoxon rank sum tests. Logistic regression models were run for each outcome to estimate odds ratios and 95% confidence intervals. Two sets of models were generated. For the first set of models, only early variables (ie, variables available up to the time of initiation of the THAPCA-IH temperature management intervention) were considered. For the second set of models, both early and late variables (ie, variables available through day 7) were considered. Variables that had a univariate p value less than 0.1 were entered into each model by using a stepwise selection approach and only those variables with a p value less than 0.05 were retained in the final models. All analyses were completed by using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Of 56 children receiving open-chest CPR, 34 (61%) were male, and 43 (77%) were younger than 1 year (Supplemental Table 1). Nine children (16%) were underweight and 7 (13%) were obese. Seven children (13%) had prearrest technology dependence and 8 (14%) had a previous ICU admission during the hospitalization. Fifty-five children (98%) had at least one preexisting condition. Fifty-three children (95%) had a preexisting cardiac condition (17 with single ventricle), 18 (32%) had a prenatal condition, 12 (21%) had a gastrointestinal condition, 11 (20%) had a respiratory condition, 10 (18%) had a renal condition, 8 (14%) had a neurologic condition, 2 (4%) had pulmonary hypertension, and 16 (29%) had other condition.

Forty-nine children (88%) were postoperative from cardiac surgery at the time of open-chest CPR (Supplemental Table 2). Of the 7 children (13%) who were not postoperative from cardiac surgery, 3 underwent primary sternotomy for central cannulation for ECMO. One child received open-chest compressions during a cardiac operation, one during an operation for excision of an extralobar sequestration, and one after an operation for congenital chylothorax complicated by severe bleeding. One additional child received open-chest CPR through a resternotomy after remote cardiac surgery (ie, cardiac surgery during a prior hospitalization) and pacemaker placement.

Primary cause of arrest was deemed a cardiovascular event for 49 children (88%) and a respiratory event for 7 children (13%) (Supplemental Table 2). Initial cardiac rhythm at the time chest compressions were started was bradycardia for 30 (54%), pulseless electrical activity for 16 (29%), ventricular tachycardia/fibrillation for 6 (11%), and asystole for 3 (5%). Sixteen children (29%) had at least one defibrillation attempt. Thirty-one children (55%) received chest compressions for more than 30 minutes; for all children, the median duration of chest compressions was 32.5 minutes (interquartile range: 16.8 to 46.0 minutes). The number of epinephrine doses was more than 8 for 16 children (29%), and the epinephrine dosing interval was 5 minutes or more for 32 children (57%). Fifty-five children (98%) had intravenous access at the time of arrest, and 45 (80%) were intubated. Cardiac arrest occurred in the ICU for 43 children (77%), the operating room for 10 (18%), and a non-ICU inpatient ward for 3 (5%).

Twenty-five children (45%) were managed after the arrest with therapeutic hypothermia and 31 (55%) with therapeutic normothermia (Supplemental Table 2). Forty-four children (79%) were receiving ECMO at the time of initiation of the temperature management intervention (ie, ECMO cannulation either during CPR or within 6 hours of return of spontaneous circulation). Renal replacement therapy was used in 17 children (30%) and clinical or electrographic seizures were documented in 7 (13%) between the time of randomization in the THAPCA-IH trial through day 5. Fifty-four children (96%) received blood products between the time of randomization through day 7. Of these, 52 children (96%) received red blood cells, 49 (91%) received platelets, 35 (65%) received fresh frozen plasma, and 29 (54%) received cryoprecipitate. Fourteen children (25%) had a culture-positive infection. Of these children 9 (64%) had respiratory infection, 4 (29%) had urinary tract infection, and 1 (7%) had bloodstream infection. Nine children (16%) had a serious arrhythmia. Lactate declined to less than 2 mmol/L in 42 children (75%) within 48 hours of the start of the temperature management intervention. Thirty-three children (59%) survived to 12 months, 22 (41%) survived to 12 months with VABS-II decreased by no more than 15 points from baseline, and of those with baseline VABS-II of 70 or more points 23 (51%) survived to 12 months with VABS-II of 70 or more points. A Kaplan-Meier survival graph for all 56 children is shown in Figure 1.

Univariate Associations

Presence of a preexisting renal condition was associated with lower 12-month survival (Supplemental Table 1). Epinephrine dosing interval of 3 to 5 minutes was associated with greater 12-month survival, and failure of lactate to decline to less than 2 mmol/L within 48 hours of the start of the temperature management intervention was associated with lower 12-month survival (Supplemental Table 2). Use of ECMO and the presence of clinical or electrographic seizures were associated with lower 12-month survival with VABS-II of 70 or more points. Use of renal replacement therapy was associated with lower 12-month survival, lower 12-month survival with VABS-II decreased no more than 15 points from baseline, and lower 12-month survival with VABS-II of 70 or more points. Univariate associations between laboratory values and outcomes are shown in Supplemental Table 3.

Logistic Regression Models

Logistic regression models, including early variables (ie, variables available up to the time of initiation of the temperature management intervention), are shown in Supplemental Table 4. Presence of a preexisting renal condition was independently associated with lower

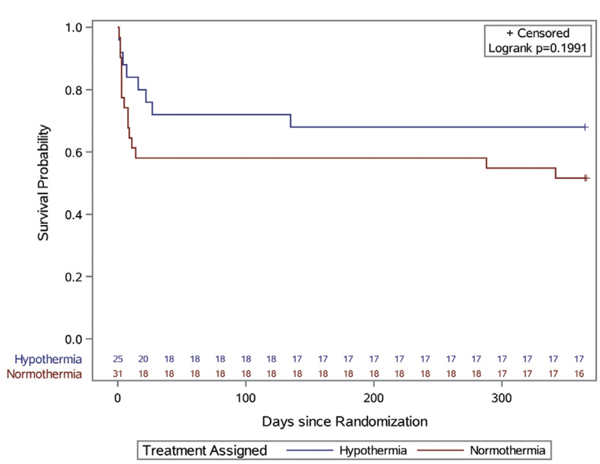

Fig 1. Kaplan-Meier estimates of survival to 1 year after cardiac arrest.

12-month survival. Use of ECMO was independently associated with lower 12-month survival with VABS-II of 70 or more points.

Logistic regression models, including early and late variables (ie, variables available through day 7), are shown in Supplemental Table 5. Higher minimum bilirubin was independently associated with lower 12-month survival. When bilirubin was excluded from the model of 12-month survival, higher minimum INR was independently associated with lower 12-month survival. Higher minimum INR was independently associated with lower 12-month survival with VABS-II decreased by no more than 15 points from baseline. Higher maximum INR and use of renal replacement therapy were independently associated with lower 12-month survival with VABS-II of 70 or more points.

Comment

Here, we report about the 1-year neurobehavioral outcomes in a cohort of children who received open-chest CPR during in-hospital cardiac arrest. Our findings demonstrate that approximately one-half of children who received open-chest CPR survived with good neurobehavioral outcome at 1 year. Most of the children in our study were postoperative from cardiac surgery at the time of open-chest CPR and cannulated for ECMO either during CPR or within 6 hours of return of spontaneous circulation. It is important to acknowledge that the children included in our study were recruited to the THAPCA-IH trial and as such were comatose after arrest. Therefore, children included in our study were likely at greater risk of neurologic disability than other children experiencing in-hospital arrest and open-chest CPR. Children participating in randomized controlled trials may also differ from children whose caregivers refuse participation in ways that are unknown.

We performed exploratory logistic regression analyses by using early variables to identify those most strongly associated with outcomes. These analyses demonstrated that preexisting renal failure was independently associated with lower 12-month survival and that the peri-resuscitation use of ECMO was independently associated with lower 12-month survival with VABS-II of 70 or more points. Several studies have shown an association between preexisting renal failure and death after in-hospital cardiac arrest [11–16]. A recent analysis of the Virtual Pediatric Systems Database between 2009 and 2014 found that among children undergoing cardiac surgical procedures (n = 26,909), preexisting renal failure was one of several factors associated with increased risk of postoperative cardiac arrest [12]. Among those with postoperative cardiac arrest, preexisting renal failure and use of postoperative ECMO were associated with increased mortality at ICU discharge [12]. Acid–base and electrolyte abnormalities are common during and after cardiac arrest. Preexisting renal failure may increase the severity of these derangements and make them difficult to treat, potentially contributing to worse outcomes. The peri-resuscitation use of ECMO in our study represents

ECMO cannulation during open-chest CPR or within 6 hours of return of spontaneous circulation. Children who require ECMO during or after CPR are likely to have persistent cardiogenic shock until the time of ECMO initiation; thus, those requiring ECMO may be more severely ill than children who do not require ECMO. Greater severity of illness may potentially explain the relation between the use of periresuscitation ECMO and lower survival with good neurobehavioral outcome at 1 year.

We also performed exploratory logistic regression analyses by using both early and late variables. Higher minimum bilirubin was independently associated with lower 12-month survival; when bilirubin was excluded from the analysis, higher minimum INR was associated with lower 12-month survival. Higher minimum INR was also independently associated with lower 12-month survival with VABS-II decreased by no more than 15 points from baseline. Higher maximum INR and use of renal replacement therapy were independently associated with lower 12-month survival with VABS-II of 70 or more points. These findings suggest that postarrest hepatic or renal dysfunction may contribute to reduced 1-year survival with good neurobehavioral outcome. These findings are consistent with prior reports demonstrating an association between end-organ injury after extracorporeal CPR (ECPR) and worse outcomes at hospital discharge [17–20].

Some important variables not associated with outcomes in our study include the presence of single ventricle lesions, duration of cardiac compressions, and occurrence of postarrest infection. Although outcomes of children with single ventricle lesions receiving open-chest CPR have not been explicitly reported, studies of the use of ECPR (open- and closed-chest) have suggested higher mortality at hospital discharge for children with single ventricle lesions than with biventricular lesions [18, 21–23]. Significant late attrition after ECPR has also been reported for children with single ventricle lesions [24]. Longer duration of CPR is a known predictor of outcomes after in-hospital cardiac arrest [11, 25, 26]. However, conflicting findings exist in the setting of ECPR [20, 22, 24, 27]. Similar to our findings, prior reports that failed to identify CPR duration as a predictor of outcome often had long median durations of CPR (eg, >30 minutes). A recent study found postarrest infection in 56% of children with in-hospital cardiac arrest and return of spontaneous circulation; 82% of infected children had a positive culture [28]. Similar to our findings, respiratory infections were most common, and no association with death was identified. Difficulty interpreting the significance of positive respiratory cultures in intubated children may confound associations with outcomes [29]. Data about wound or mediastinal infections were not collected in the THAPCA-IH trial.

Strengths of our study include the multicenter design, prospective data collection, and use of the VABS-II to measure neurobehavioral outcomes 1 year after open-chest CPR for in-hospital cardiac arrest. Limitations include the potential bias inherent in including children recruited to a randomized controlled trial; specifically, all children recruited to the THAPCA-IH trial were comatose after arrest with high risk of neurologic disability. Of 56 children receiving open-chest CPR, only 33 survived 12 months, limiting the number of neurobehavioral assessments performed. Other limitations include the large number of variables evaluated, as well as lack of data on some potentially important variables. For example, most children receiving open-chest CPR were postoperative from cardiac surgery and received periresuscitation ECMO; however, data about cardiac diagnoses, surgical complexity, and details of ECMO cannulation and management were not available in the THAPCA-IH database. Some children may have received closed-chest CPR before open-chest CPR during the cardiac arrest event; the proportion of time spent undergoing closed- and open-chest compressions for these children is unknown. The number of children whose sternum was open before arrest while waiting for delayed sternal closure is also unknown. Data about the occurrence of central nervous system stroke were not available. Of importance, although several associations were observed, causation cannot be inferred. Our findings can be useful to help guide clinical decision making and in counseling parents. For example, the finding that approximately one-half of children survived with good neurobehavioral outcome after open-chest CPR could be shared with parents when discussing prognosis. Similarly, clinicians and parents could consider the identified risk factors for worse outcomes when discussing options for care.

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