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## Clinical paper

### Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children<sup>☆</sup>

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#### ABSTRACT

**Aim:** To describe the 1-year neurobehavioral outcome of survivors of cardiac arrest secondary to drowning, compared with other respiratory etiologies, in children enrolled in the Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) trial.

**Methods:** Exploratory analysis of survivors (ages 1–18 years) who received chest compressions for  $\geq 2$  min, were comatose, and required mechanical ventilation after return of circulation (ROC). Participants recruited from 27 pediatric intensive care units in North America received targeted temperature management [therapeutic hypothermia (33 °C) or therapeutic normothermia (36.8 °C)] within 6 h of ROC. Neurobehavioral outcomes included 1-year Vineland Adaptive Behavior Scales, Second Edition (VABS-II) total and domain scores and age-appropriate cognitive performance measures (Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence).

**Results:** Sixty-six children with a respiratory etiology of cardiac arrest survived for 1-year; 60/66 had broadly normal premorbid functioning (VABS-II  $\geq 70$ ). Follow up was obtained on 59/60 (30 with drowning etiology). VABS-II composite and domain scores declined significantly from premorbid scores in drowning and non-drowning groups ( $p < 0.001$ ), although declines were less pronounced for the drowning group. Seventy-two percent of children had well below average cognitive functioning at 1-year. Younger age, fewer doses of epinephrine, and drowning etiology were associated with better VABS-II composite scores. Demographic variables and treatment with hypothermia did not influence neurobehavioral outcomes.

**Conclusions:** Risks for poor neurobehavioral outcomes were high for children who were comatose after out-of-hospital cardiac arrest due to respiratory etiologies; survivors of drowning had better outcomes than those with other respiratory etiologies.

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## Introduction

Multicenter or population-based studies of pediatric out-of-hospital cardiac arrest (OHCA) are limited. In a recent, prospective, multicenter, randomized controlled trial, Therapeutic Hypothermia after Pediatric Cardiac Arrest, Out-of-Hospital (THAPCA-OH), the efficacy of two targeted temperature management strategies [therapeutic hypothermia (33 °C) to therapeutic normothermia

(36.8 °C) was examined. Children recruited to THAPCA-OH were comatose and required mechanical ventilation after return of circulation (ROC), and were at high risk for neurologic disability. Trial results showed that neither treatment arm conferred a significant benefit on survival with favorable functional outcome.<sup>1</sup>

Planned secondary analyses of this trial found substantial neurobehavioral morbidity in survivors one year later.<sup>2,3</sup> Neurobehavioral outcomes included caregiver-reported functional skills in a range of domains [Vineland Adaptive Behavior Scales, Second Edition (VABS-II)] and age-appropriate cognitive performance measures (Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence). While many children displayed severe to profound impairments on these measures, there was a range of outcomes; half functioned broadly within normal limits (within 2 SD of VABS-II means) and one third functioned similarly well on cognitive testing. Variables associated with worse outcome included older age and respiratory (compared with cardiac) etiologies. Neither reported outcomes separately for children with OHCA secondary to drowning or other respiratory etiologies.

Drowning cases enrolled in THAPCA-OH were described in secondary studies.<sup>4,5</sup> Hypothermia did not confer significant outcome benefit in comparison with normothermia and there was a high rate of culture-proven bacterial infection in both groups.<sup>4</sup> Among respiratory etiologies, drowning was associated with better outcomes.<sup>5</sup> Similarly, in an observational cohort, children with drowning etiologies were more likely to survive to hospital discharge compared to all other OHCA etiologies.<sup>6</sup> This cohort included children with lower risk for poor neurological outcome than those enrolled in the THAPCA-OH trial; all children with  $\geq 1$  min of chest compressions were included (versus  $\geq 2$  min with coma after ROC in THAPCA-OH). Detailed neurobehavioral outcomes were not examined in these reports.

In a broader group of children with OHCA due to drowning, who received emergency medical services, most had unfavorable short-term neurologic outcome.<sup>7</sup> Long-term outcomes, however, varied in a similar group. Suominen et al. explored neurobehavioral outcome several years after OHCA due to drowning in children resuscitated and then admitted to intensive care. In that group, 57% had neurological dysfunction and 40% had below average full-scale IQs<sup>8</sup>; longer submersion time was associated with worse cognitive outcome. There is also evidence that length of resuscitation is predictive of global outcome after drowning in children.<sup>9</sup>

To date, no study has examined detailed neurobehavioral outcomes one year after pediatric OHCA due to drowning or other respiratory etiologies, in children who remained comatose following ROC. Better understanding of the range of outcomes and outcome predictors in these children would be helpful for neuroprognostication. The objective of this study, restricted to a distinct and well-characterized sub-group of THAPCA-OH enrolled subjects who survived for at least one year, is to compare neurobehavioral outcomes in OHCA cases due to drowning with those due to other respiratory etiologies. Based on the limited literature available, we hypothesized that children with OHCA due to drowning would have better neurobehavioral outcomes than those with OHCA due to other respiratory etiologies.

## Methods

### Study setting and population

The THAPCA-OH trial was conducted in 36 pediatric intensive care units (PICUs) in the United States (U.S.) and Canada from September 1, 2009 through December 31, 2012. Details of the THAPCA-OH trial were previously published.<sup>10,11</sup> The trial was approved by the Institutional Review Boards at all sites, the Data Coordinating Center, and Outcome Center.

Children  $>48$  h and  $<18$  years of age who had an OHCA with chest compressions for  $\geq 2$  min, and required mechanical ventilation after ROC met the original trial inclusion criteria. Major exclusion criteria for the THAPCA-OH Trial included the inability to be randomized within 6 h of ROC, a Glasgow Coma Scale motor score of 5 or 6, a decision by clinicians to withhold aggressive treatment, OHCA due to trauma, and drowning in ice water. The inclusion and exclusion criteria are detailed in the primary outcome paper Supplemental Appendix.<sup>1</sup>

Of the 66 survivors who had respiratory etiologies, 60 had pre-OHCA VABS-II scores  $\geq 70$  and were eligible for the THAPCA-OH primary outcome analysis. This report analyzes 1-year neurobehavioral outcomes in 59 of these 60 survivors who were recruited from 27 of the 36 THAPCA-OH PICU sites. Children were grouped based on reported OHCA etiology (drowning versus other respiratory etiology).

### Measures

#### Neurobehavioral functioning

*Vineland Adaptive Behavior Scales, Second Edition (VABS-II)*<sup>12</sup>. VABS-II measures caregiver report of functional skills and provides age-corrected standard scores [mean = 100, standard deviation (SD) = 15] in four domains (communication, daily living, socialization, motor skills) and an overall adaptive behavior composite. Higher scores denote better functioning. In THAPCA-OH, a favorable outcome was defined as a score within 2SD of the age-corrected standard score mean ( $\geq 70$ ). Each domain includes several subdomains with developmentally sequenced items, starting with skills typically observed in infancy. VABS-II includes a parent/caregiver rating form and a survey interview (using caregiver as informant) that yield comparable scores.<sup>12</sup>

#### Cognitive performance

*Wechsler Abbreviated Scale of Intelligence (WASI)*<sup>13</sup>. WASI measures intellectual or general cognitive functioning. Normative data are based on a standardization sample highly representative of the English-speaking United States population aged from 6 to 89. The Vocabulary subtest requires individuals to orally define words. The Matrix Reasoning subtest, a measure of non-verbal fluid reasoning, requires individuals to view incomplete gridded patterns and select correct responses. Age-corrected standardized t-scores are available for both. When combined, these subtests yield age-corrected standard scores (mean = 100, SD = 15) for general intellectual functioning (Full Scale IQ).

*Mullen Scales of Early Learning (Mullen)*<sup>14</sup>. The Mullen, a measure of cognitive functioning designed for infants and young children, has four scales (visual reception, fine motor, receptive language, and expressive language). Normative data are available through age 5-years-8-months. Age-corrected standardized scores are available for each scale as t-scores and for overall early learning composite as a standard score.

For this report, all t-scores (Mullen and WASI) and v-scores (VABS-II) were transformed to standard scores. Scores  $>115$  are above average, 85–115 are average, 70–84 are below average, and 50–69 are well below average. The lowest possible Mullen composite score is 49. For Mullen scales, raw scores below the lowest score on the normative table for age were referred to as lowest possible scores.

#### Other descriptive measures

*Family Assessment Device*<sup>15</sup>. Pre-OHCA family functioning was measured using the General Functioning Scale of the Family Assess-

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