Cardiac Arrest Outcomes in Children With Preexisting Neurobehavioral Impairment

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Objectives: To describe survival and 3-month and 12-month neurobehavioral outcomes in children with preexisting neurobehavioral impairment enrolled in one of two parallel randomized clinical trials of targeted temperature management.

Design: Secondary analysis of Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital and Out-of-Hospital trials data.

Setting: Forty-one PICUs in the United States, Canada, and United Kingdom.

Patients: Eighty-four participants (59 in-hospital cardiac arrest and 25 out-of-hospital cardiac arrest), 49 males, 35 females, mean age 4.6 years (SD, 5.36 yr), with precardiac arrest neurobehavioral impairment (Vineland Adaptive Behavior Scales, Second Edition composite score < 70). All required chest compressions for greater than or equal to 2 minutes, were comatose and required mechanical ventilation after return of circulation.

Interventions: Neurobehavioral function was assessed using the Vineland Adaptive Behavior Scales, Second Edition at baseline (reflecting precardiac arrest status), and at 3 and 12 months postcardiac arrest, followed by on-site cognitive evaluation. Vineland Adaptive Behavior Scales, Second Edition norms are 100 (mean) $\pm$ 15 (SD); higher scores indicate better function. Analyses evaluated survival, changes in Vineland Adaptive Behavior Scales, Second Edition, and cognitive functioning.

Measurements and Main Results: Twenty-eight of 84 (33%) survived to 12 months (in-hospital cardiac arrest, 19/59 (32%); out-of-hospital cardiac arrest, 9/25 [36%]). In-hospital cardiac arrest (but not out-of-hospital cardiac arrest) survival rate was significantly lower compared with the Therapeutic Hypothermia after Pediatric Cardiac Arrest group without precardiac arrest neurobehavioral impairment. Twenty-five survived with decrease in Vineland Adaptive Behavior Scales, Second Edition less than or equal to 15 (in-hospital cardiac arrest, 18/59 (31%); out-of-hospital cardiac arrest, 7/25 [28%]). At 3-months postcardiac arrest, mean Vineland Adaptive Behavior Scales, Second Edition scores declined significantly (–5; SD, 14; $p < 0.05$). At 12 months, Vineland Adaptive Behavior Scales, Second Edition declined after out-of-hospital cardiac arrest (–10; SD, 12; $p < 0.05$), but not in-hospital cardiac arrest (0; SD, 15); 43% (12/28) had unchanged or improved scores.

Conclusions: This study demonstrates the feasibility, utility, and challenge of including this population in clinical neuroprotection trials. In children with preexisting neurobehavioral impairment, one-third survived to 12 months and their neurobehavioral outcomes varied broadly. (*Pediatr Crit Care Med* 2019; XX:00–00)

Key Words: cardiac arrest; neurobehavioral; outcome; pediatrics; preexisting impairment

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Additional members of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trial Investigators are listed in **Supplemental Appendix 1** (Supplemental Digital Content 7, http://links.lww.com/PCC/A919).

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Cardiac arrest (CA) in children often results in death or neurologic impairment. A significant proportion of those who sustain a CA have preexisting neurobehavioral impairment (1, 2). Although inclusion of persons with disabilities in clinical trials has been encouraged to improve generalizability of results (3), most pediatric CA outcome studies do not describe pre-CA neurobehavioral functioning (4–10), and when it is reported, a global measure is used to categorize function (1, 2). Also, studies reporting detailed neurobehavioral outcomes have excluded subjects with known significant preexisting developmental disabilities (11–15).

Recently, two parallel multicenter randomized clinical trials (Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital [THAPCA-IH, NCT00880087] and Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital [THAPCA-OH, NCT00878644]) evaluated two targeted temperature management strategies (therapeutic hypothermia [33°C] and therapeutic normothermia [36.8°C]) in children who were comatose after in-hospital cardiac arrest (IH-CA) or out-of-hospital cardiac arrest (OH-CA) (16, 17). Detailed pre-CA neurobehavioral functioning was obtained soon after enrollment, based on caregiver report using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II); scores less than 70 indicated pre-CA neurobehavioral impairment. Favorable primary outcome was defined as 1-year survival without significant neurobehavioral impairment (VABS-II ≥ 70).

Children with preexisting neurobehavioral impairment were included in both THAPCA-IH and THAPCA-OH trials but excluded from primary outcomes, since their baseline scores were below the threshold for 12-month favorable outcome. However, they were included in secondary outcome analyses (survival, change in VABS-II). Hypothermia did not confer a significant benefit in either trial on 1-year survival with favorable functional outcome, survival alone, or change in VABS-II (16, 17). Secondary analyses of detailed neurobehavioral outcomes in 12-month survivors focused on those without significant pre-CA neurobehavioral impairment (13–15). The principal aim of this secondary analysis of THAPCA-IH/OH data are to report survival, detailed neurobehavioral, and cognitive outcomes 1-year after CA in children with preexisting neurobehavioral impairment (pre-CA VABS-II < 70). Complementary aims are to explore differences in outcome in those with pre-CA neurobehavioral impairment after IH-CA versus OH-CA and those treated with normothermia versus hypothermia. Additionally, we evaluate whether survival differed between THAPCA participants with and without pre-CA neurobehavioral impairment.

METHODS

Participants

Six-hundred twenty-four children (THAPCA-IH 329, THAPCA-OH 295), greater than or equal to 48 hours and less than 18 years old, who received greater than or equal to 2 minutes of chest compressions, required mechanical ventilation and were comatose after CA, were enrolled in 41 PICUs in the United States, Canada, and United Kingdom; data were collected from 2009 to 2015. The studies were approved by Institutional Review Boards at each site. Major exclusion criteria included inability to be randomized within 6 hours of return of circulation, a Glasgow Coma Scale motor score of 5 or 6 (age-appropriate lateralized response to pain), trauma, progressive degenerative encephalopathy, and decision to withhold aggressive treatment. Full inclusion and exclusion criteria, randomization, and enrollment details were reported (16, 17).

At enrollment, 85 of 624 (13.6%) (THAPCA-IH 60/329 [18.2%], THAPCA-OH 25/295 [8.5%]) with pre-CA VABS-II composite scores less than 70 (or Pediatric Cerebral Performance Category [PCPC] and/or Pediatric Overall Performance Category [POPC] scores greater than or equal to 3 in eight subjects with missing pre-CA VABS-II) were ineligible for the THAPCA primary outcome. One case was excluded after diagnosis of a progressive degenerative encephalopathy. At 12-month follow-up, vital status was known for all 84 participants; 28 survived (THAPCA-IH 19, THAPCA-OH 9) and pre-CA VABS-II was obtained for all survivors. This report analyzes outcomes in these 84 cases.

Assessment Measures

Family Functioning. Pre-CA family functioning was measured using the General Functioning Scale of the "Family Assessment Device"; possible scores 0–4; greater than or equal to 2 indicates abnormal functioning (18).

Global Functioning Measures. "PCPC and POPC" (19, 20). PCPC measures neurologic functioning. POPC measures overall health (including neurologic functioning). These clinician-rated scales have been recommended for reporting outcome following pediatric CA (21).

Neurobehavioral Outcome Measures. VABS-II (22) measures functional skills and provides age-corrected standard scores (mean, 100; SD, 15) in four domains (communication, daily living, socialization, and motor skills) and an overall adaptive behavior composite. Each domain includes subdomains with developmentally sequenced items, starting with skills typically observed in infancy. VABS-II includes a caregiver rating form and a survey interview (using caregiver as informant) that yield comparable scores (22). Description of developmental skills typical of score ranges at different ages is available (14).

"Wechsler Abbreviated Scale of Intelligence (WASI)" (23). WASI measures intellectual or general cognitive functioning (standardized for 6–89 yr old), including Vocabulary subtest and Matrix Reasoning (non-verbal) subtest. Age-corrected standardized scores were calculated for each subtest individually and combined for general intellectual functioning (Full Scale Intelligence Quotient).

"Mullen Scales of Early Learning" (24). The Mullen, a measure of cognitive functioning designed for infants and young children, has 4 scales (visual reception, fine motor, receptive language, and expressive language). Normative data are available through age 5 year 8 months. Age-corrected standardized scores are available for each scale and for overall early learning composite.

All standardized scores were transformed to standard scores; we defined scores 85–115 as average, 70–84 below average, 50–69 impaired, and less than 50 severely impaired. This definition for severely impaired was chosen because the lowest possible Mullen composite score is 49, and the lowest possible VABS-II composite varies by age. For Mullen scales, raw scores below the lowest score on the normative table for age were referred to as lowest possible scores.

Procedures

Informed consent was signed by a caregiver. Within 24 hours of enrollment, and after review of instructions with a site research coordination, a primary caregiver completed the VABS-II caregiver rating form to assess pre-CA functioning. The research coordinators reviewed the VABS-II form for completion and response accuracy, collected demographics, CA characteristics, and rated pre-CA neurologic (PCPC) and overall functioning (POPC).

Three and 12-months post-CA, a trained research assistant at one site (Kennedy-Krieger Institute, Baltimore, MD), unaware of treatment group assignment, conducted a semi-structured telephone interview to assess neurobehavioral function (including VABS-II). Subsequently, when feasible, children participated in on-site cognitive testing. Children greater than or equal to 6 years old who were reported to have no consistent means of functional communication on the 12-month VABS-II did not undergo additional testing and were assigned lowest possible scores for analyses.

Statistical Analysis

Survival at 12 months post-CA was compared between those children with and without pre-CA neurobehavioral impairment using Fisher exact test. Distributions of continuous variables were compared between the THAPCA-IH and THAPCA-OH groups using *t* tests and Wilcoxon rank-sum tests. Categorical variables were compared between the groups using Fisher exact test. Change in VABS-II scores was calculated (3 mo, baseline score; 12 mo, baseline score; and 12 mo, 3-mo score). Signed-rank tests evaluated differences between two continuous variables (e.g., between baseline and 12-mo scores). All analyses were performed using SAS software, Version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Sample Characteristics

Sample characteristics are reported in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A913). Average age at randomization was 4 years, 7 months; with half less than 2 years old. Mean pre-CA VABS-II composite score was 57.6. The majority had moderate or severe impairment on the PCPC/POPC. All but one participant had at least one preexisting medical condition. The most common preexisting conditions were neurologic, cardiac, and lung or airway disease. Details of preexisting conditions are presented in **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/PCC/A914).

In IH-CA (relative to OH-CA), preexisting cardiac condition was more common, tracheostomies were less common, number of epinephrine doses was higher, duration of chest compressions was less, and extracorporeal membrane oxygenation was used exclusively in this group. Etiology of CA differed significantly (cardiac most common etiology for IH-CA, respiratory for OH-CA).

Twenty-eight of 84 (33%) survived to 12 months. Survival between those with IH-CA versus OH-CA was similar (IH-CA, 19/59 (32%); OH-CA, 9/25 (36%); $p = 0.80$). Survival with decrease in VABS-II score from baseline less than or equal to 15 was also similar (IH-CA, 18/59 (31%); OH-CA, 7/25 (28%); $p = 1.00$).

In survivors, mean 12-month post-CA VABS-II composite score was 54.4. The percentage of those classified as moderate, severe, or coma (PCPC and POPC ≥ 3) increased. Comparing OH-CA to IH-CA survivors, the OH-CA group was significantly more impaired, based on the VABS-II ($p < 0.001$), PCPC ($p = 0.01$), and POPC ($p = 0.02$) (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A913). Also, clinically significant new comorbidities developed post-CA. In 12-month survivors, seven of 11 tracheostomies and 10 of 20 gastrostomy tubes were not present pre-CA.

Survival between targeted temperature management treatment groups was similar (hypothermia, 17/44 (38.6%); normothermia, 11/40 (27.5%); $p = 0.36$). Survival with decrease in VABS-II score from baseline less than or equal to 15 was also similar (hypothermia, 15/44 (34%); normothermia, 10/40 (25%); $p = 0.47$).

There were no significant differences in demographics, pre-CA functioning, or CA characteristics (primary etiology of CA, number of epinephrine doses, cardiopulmonary resuscitation duration, or randomization treatment) between survivors and nonsurvivors, nor between treatment groups (hypothermia or normothermia) (data not shown).

In the only analyses using the THAPCA group without pre-CA neurobehavioral impairment for comparison (**Table 1**), IH-CA (but not OH-CA) survival rate was significantly lower ($p = 0.014$) for those with, compared with those without pre-CA neurobehavioral impairment (age was not significantly different between these two groups; $p = 0.14$).

Neurobehavioral Outcomes in Survivors

Table 2 displays mean pre-CA, 3-month and 12-month VABS-II scores (composite, domains, and subdomains), and change scores. Scores declined significantly from pre-CA to 3-months for the VABS-II adaptive behavior composite, two domains (daily living and motor functioning), and five subdomains (personal and domestic [daily living], play and leisure [socialization], and fine and gross [motor functioning]). VABS-II scores were significantly more impaired at 12 months compared with pre-CA functioning for only one domain (daily living), and three subdomains (personal [daily living], fine

TABLE 1. Alive at 12 Months, Comparing Groups Based on Precardiac Arrest Vineland Adaptive Behavior Scales, Second Edition Adaptive Behavior Composite

Trial Group	Pre-CA VABS ≥ 70, *n* (%)	Pre-CA VABS < 70, *n* (%)	*p*
IH	135/267 (50.6)	19/59 (32.2)	0.014[a]
OH	87/262 (33.2)	9/25 (36.0)	0.826[a]
Combined OH/IH	222/529 (42.0)	28/84 (33.3)	0.152[a]

CA = cardiac arrest, IH = in-hospital, OH = out-of-hospital, VABS = Vineland Adaptive Behavior Scale.

[a]Fisher exact test.

[motor functioning], and expressive [communication]). There were no significant changes from 3 to 12 months.

Given significant differences in sample characteristics between the IH-CA and OH-CA groups, their 12-month neurobehavioral outcomes were explored separately by evaluating change from baseline (**Table 3**). In the OH-CA group, VABS-II composite, two domains (daily living, motor functioning), and six subdomains (expressive [communication], personal [daily living], interpersonal relationship, play and leisure [socialization], and gross and fine [motor functioning]) declined significantly. In the IH-CA group, only one domain (daily living) and one subdomain (personal [daily living]) declined significantly between pre-CA and 12 months.

Supplemental Figure 1 (Supplemental Digital Content 3, http://links.lww.com/PCC/A915; **legend**, Supplemental Digital Content 8, http://links.lww.com/PCC/A920) shows the

TABLE 2. Vineland Adaptive Behavior Scales, Second Edition Mean (SD) Adaptive Behavior Composite, Domain, and Subdomain Scores in 12-Month Survivors (In-Hospital and Out-of-Hospital Trials Combined)

Vineland Adaptive Behavior Scales, Second Edition	*n*[a]	Pre-CA	Month 3	Month 12	Pre-CA to Month 3 Change	Pre-CA to Month 12 Change	Month 3 to Month 12 Change
Adaptive behavior composite	28	57 (9)	53 (17)	54 (18)	−5 (14)[b]	−3 (15)	1 (9)
Communication	28	59 (13)	56 (23)	57 (20)	−3 (26)	−1 (20)	1 (14)
Receptive	28	69 (14)	64 (23)	65 (23)	−6 (23)	−4 (23)	1 (11)
Expressive	28	64 (16)	59 (24)	56 (21)	−5 (24)	−8 (19)[b]	−3 (14)
Written	9	58 (11)	56 (13)	58 (16)	−4 (7)	−3 (9)	1 (5)
Daily living	28	61 (14)	52 (15)	53 (17)	−8 (16)[c]	−8 (16)[c]	0 (9)
Personal	28	61 (17)	51 (14)	53 (17)	−9 (13)[c]	−9 (14)[c]	1 (9)
Domestic	17	69 (17)	68 (22)	70 (19)	−5 (11)[b]	−7 (13)	−3 (9)
Community	17	64 (16)	63 (21)	66 (20)	−5 (14)	−6 (15)	−1 (7)
Socialization	28	63 (13)	61 (21)	65 (20)	−2 (20)	2 (19)	3 (12)
Interpersonal relationship	28	67 (14)	63 (23)	64 (23)	−5 (20)	−3 (18)	1 (10)
Play and leisure	28	68 (14)	64 (20)	64 (20)	−4 (10)[b]	−4 (11)	0 (7)
Coping skills	17	75 (14)	73 (19)	75 (18)	−4 (20)	−6 (22)	−2 (5)
Motor functioning	27	57 (14)	49 (18)	53 (20)	−7 (12)[c]	−3 (15)	3 (12)
Gross	27	62 (11)	57 (14)	59 (15)	−4 (10)[b]	−3 (13)	2 (12)
Fine	27	68 (17)	59 (21)	60 (23)	−9 (15)[c]	−7 (17)[b]	1 (10)

CA = cardiac arrest.

[a]*n* with both pre-CA and month 12 assessment. One subject with the pre-CA assessment did not complete the month 3 assessment. The *n*'s also vary because of age differences and missing data. Domestic, community, and coping skills subdomains are not administered to children < 1 yr old. Written subdomain is not administered to children < 3 yr old.

[b]$p < 0.05$.

[c]$p < 0.01$.

All *p* values from the signed-rank test.

TABLE 3. Mean (SD) Vineland Adaptive Behavior Scales, Second Edition Scores at Precardiac Arrest and 12-Month Follow-Up and Mean (SD) Change (Precardiac Arrest Vineland Adaptive Behavior Scale < 70) by Trial Group

Vineland Adaptive Behavior Scales, Second Edition	n^a	In-Hospital Group, $n = 19$			Out-of-Hospital Group, $n = 9$		
		Pre-CA Scores	Follow-Up Scores	Change	Pre-CA Scores	Follow-Up Scores	Change
Adaptive behavior composite	28	61 (9)	61 (18)	0 (15)	51 (7)	41 (9)	−10 (12)[b]
Communication	28	63 (13)	66 (19)	3 (20)	50 (10)	39 (8)	−11 (16)
Receptive	28	73 (15)	73 (22)	0 (24)	62 (8)	48 (14)	−14 (19)
Expressive	28	70 (13)	66 (18)	−4 (18)	52 (16)	36 (7)	−16 (19)[b]
Written	9	60 (15)	63 (19)	−3 (14)	56 (9)	52 (8)	−4 (4)
Daily living	28	64 (15)	58 (18)	−7 (18)[b]	52 (7)	42 (10)	−10 (11)[b]
Personal	28	65 (19)	58 (18)	-8 (16)[c]	52 (9)	42 (7)	−11 (8)[c]
Domestic	17	69 (19)	74 (19)	−3 (12)	69 (15)	61 (18)	−14 (13)
Community	17	70 (15)	71 (20)	−6 (18)	56 (15)	56 (19)	−6 (11)
Socialization[d]	28	66 (14)	72 (20)	6 (20)	55 (9)	49 (11)	−7 (13)
Interpersonal relationship[d]	28	72 (14)	73 (20)	2 (18)	58 (10)	44 (12)	−14 (14)[b]
Play and leisure	28	72 (14)	70 (20)	−1 (12)	60 (11)	52 (13)	−8 (8)[b]
Coping skills	17	80 (17)	80 (19)	−5 (27)	69 (7)	63 (11)	−7 (15)
Motor functioning	27	60 (14)	60 (19)	0 (15)	51 (10)	38 (13)	−11 (11)[c]
Gross	27	64 (12)	64 (16)	−1 (14)	56 (8)	48 (5)	−8 (7)[b]
Fine[d]	27	71 (18)	69 (21)	−2 (16)	61 (15)	41 (12)	−18 (14)[b]

CA = cardiac arrest.

[a] n with both pre-CA and 12 mo assessment. The n's also vary because of age differences and missing data. Domestic, community, and coping skills subdomains are not administered to children < 1 yr old. Written subdomain is not administered to children < 3 yr old.

[b] $0.01 \le p < 0.05$ from a signed-rank test comparing pre-CA and follow-up scores.

[c] $0.001 \le p < 0.01$ from a signed-rank test comparing pre-CA and follow-up scores.

[d] $p < 0.05$ from a Wilcoxon rank-sum test comparing the 12 mo change in scores between trial groups.

distribution of VABS-II scores. The VABS-II composite (pre-CA to 12 mo) was unchanged or improved in 12 of 28 (43%) (IH-CA, 10/19; OH-CA, 2/9), declined less than or equal to 15 points in 13 of 28 (46%) (IH-CA, 8/19; OH-CA, 5/9), or declined greater than 15 points in three of 28 (11%) (IH-CA, 1/19; OH-CA, 2/9). None of the nine subjects with pre-CA VABS-II scores less than 55 (> 3 SD), declined greater than 15 points (range, +8 to –14) (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/PCC/A916; legend, Supplemental Digital Content 8, http://links.lww.com/PCC/A920). Of those who improved, five attained VABS-II scores within the unimpaired range (≥ 70) at 12 months, including two whose scores increased over 20 points into the average range (VABS-II composites = 88, 89, age at randomization 1.7 and 1.4 yr, respectively).

Supplemental Figure 3 (Supplemental Digital Content 5, http://links.lww.com/PCC/A917; legend, Supplemental Digital Content 8, http://links.lww.com/PCC/A920) shows the distribution of PCPC scores at 3 and 12 months, compared with the pre-CA PCPC. At 3-months, no one improved. At 12 months, two improved, eight were unchanged, and 18 declined 1–3 categories (–1, $n = 9$; –2, $n = 8$; and –3, $n = 1$). Of those who were unchanged, seven of eight were severely impaired (PCPC 4) pre-CA. Of those with pre-CA (PCPC = 1–3), 17 of 20 (85%) declined at least one category, whereas in those with pre-CA (PCPC = 4) (severe impairment), one of eight declined one category, and seven of eight were unchanged.

Four survivors were rated in coma (PCPC = 5) at hospital discharge. At 12 months, one remained in coma (PCPC = 5), two had severe disability (PCPC = 4), and one was classified with moderate disability (PCPC = 3).

Cognitive Outcomes

Of the 20 survivors less than 6 years old, 16 (IH-CA, 12; OH-CA, 4) completed testing; two were not offered evaluations (U.K. sites), and two were lost to on-site testing follow-up. Lowest possible scores were received by 12 of 16 (75%) on the Mullen composite; by 10 or 11 of 16 on the 4 Mullen scales

TABLE 4. Mullen Scales of Early Learning Composite and Scale Scores for Children Less Than 6 Years Old at Follow-Up

Score Range	Early Learning Composite, *n* (%)	Visual Reception[a], *n* (%)	Fine Motor[a], *n* (%)	Receptive Language[a], *n* (%)	Expressive Language[a], *n* (%)
Lowest possible score	12 (75)	10 (63)	11 (69)	10 (63)	10 (63)
50–69 (well below average)	2 (13)	4 (25)	3 (19)	4 (25)	2 (13)
70–84 (below average)	0 (0)	0 (0)	0 (0)	1 (6)	3 (19)
85–115 (average)	2 (13)	2 (13)	2 (13)	1 (6)	1 (6)

[a]Scores were transformed to correspond to a scale with mean 100 and SD 15.
Combined in-hospital ($n = 12$) and out-of-hospital ($n = 4$).

(**Table 4**). Due to this distribution, developmental quotients (developmental age/chronologic age × 100) were calculated for Mullen Scale scores, to more fully understand the range of outcomes. Five of 16 (31%) had developmental quotients less than 20 on all 4 scales, reflecting very profound impairment (**Supplemental Fig. 4**, Supplemental Digital Content 6, http://links.lww.com/PCC/A918; legend, Supplemental Digital Content 8, http://links.lww.com/PCC/A920).

Of eight participants greater than or equal to 6 years old at 12-month follow-up, seven had no consistent means of functional communication (based on the 12-mo VABS-II) and did not undergo cognitive testing. The one who completed testing received the lowest possible score (55) for Full Scale IQ and the two WASI subtests.

DISCUSSION

This study describes outcomes in a unique cohort of children with pre-CA neurobehavioral impairment, who incurred IH-CA or OH-CA, were successfully resuscitated, were initially comatose post-resuscitation, and enrolled in targeted temperature management clinical trials. One-third survived to 1-year post-CA; neither targeted temperature management group (hypothermia vs normothermia) nor location of CA (IH vs OH) was associated with survival. IH-CA (but not OH-CA) survival rate was significantly lower compared with the THAPCA group without pre-CA neurobehavioral impairment. In survivors, significant declines in neurobehavioral function (pre-CA to 3 mo and pre-CA to 12 mo) were noted, without significant change from 3 to 12 months. Declines were more pronounced after OH-CA than IH-CA. Yet, 43% remained unchanged or had measured improvements.

Survival rates after CA in children vary depending on a multiplicity of factors but are typically higher after IH-CA than OH-CA (1). However, in this group, IH-CA and OH-CA survival rates were similar, and IH-CA survival was significantly lower than that for the THAPCA group without pre-CA neurobehavioral impairment. The increased medical complexity of this cohort may partially explain the lower survival rate after IH-CA. Many had multisystem disease, including genetic and congenital cardiac disorders commonly associated with developmental disabilities. All but one participant (99%) had preexisting conditions, compared with 48.5% (OH-CA) and 90.9% (IH-CA) for all THAPCA enrollees (25, 26). The medical complexity of this group highlights one of the challenges of their inclusion in clinical trials, as survival and neurobehavioral baseline and outcomes are not only related to CA and its treatment, but also to other medical morbidities.

Our results confirm important differences between those with IH versus OH-CA, even when assessing only children with pre-CA neurobehavioral impairments. Similar to a cohort study of children with IH and OH-CA (1), pre-CA neurobehavioral impairment was more common in the IH than OH-CA group. Similar to the overall THAPCA population, the most common etiology of OH-CA was respiratory and cardiac in IH-CA (25, 26). Also, as in the THAPCA group without pre-CA neurobehavioral impairment (13, 14), more pronounced functional declines were discerned after OH-CA than IH-CA.

Declines in function in THAPCA survivors with pre-CA neurobehavioral impairment were less than in those without pre-CA impairment. Average 12-month VABS-II Composite mean change was 0 (IH-CA) and –10 (OH-CA) in those with pre-CA impairment, in comparison with mean declines of –12 (IH-CA) and –33 (OH-CA) in THAPCA survivors without pre-CA impairment (13, 14). In the THAPCA group without pre-CA impairment, all VABS-II scores (composite, domain, and subdomain scores) declined significantly, whereas significant changes were much less frequent in those with pre-CA impairment.

Smaller and fewer significant declines in children with pre-CA neurobehavioral impairment reflect challenges inherent in measurement of their neurobehavioral declines. Specifically, no one with a pre-CA VABS-II score greater than or equal to 3 SD below the mean (VABS-II < 55) demonstrated a decline of greater than or equal to 1 SD. Similarly, PCPC scores did not decline in those with pre-CA severe impairment. However, we identified more areas of decline after OH-CA than IH-CA, even though the mean pre-CA VABS-II in survivors was qualitatively lower in the OH-CA group (51 vs 61). Consequently, although low baseline scores may limit detection of functional declines, with increasing injury severity (as with OH-CA), change can be demonstrated. However, decreased sensitivity to change in outcome measures remains a potential obstacle to inclusion of participants with preexisting neurobehavioral impairment in primary outcomes measuring neurobehavioral function.

The VABS-II evaluates developmental domains and compares change objectively. In this study, greatest pre-CA impairment was noted on motor functioning and the least on socialization. At 12 months, daily living and motor domains showed the largest declines and socialization the smallest. In the communication domain, only the subdomain of expressive language showed a significant decline and only at 12 months. These trends may in part reflect the young age of many cases analyzed. Early identification of impairment is easier in some domains, such as "daily living and motor," since there are multiple objective milestones for young children. In contrast, identification of expressive language impairment is more evident later in development, when speech blossoms. Consequently, the expressive language impairment that became significant only at 12-months post-CA could be related to the failure of acquisition of new milestones. Similar to this group, the socialization domain declined the least in THAPCA survivors without pre-CA impairment, probably due to the easily attainable simple interactions (i.e., social smile) that form the base of abilities measured for this domain. Additionally, certain medical conditions affect specific domains. The personal subdomain of daily living is heavily weighted to eating behaviors. Consequently, those with gastrostomy tubes usually score in the impaired range. Also, tracheostomies may interfere with speech development. These significant comorbidities, gastrostomy tubes and tracheostomies, were common at 12-month follow-up, the majority of which were new post-CA.

At 12-month follow-up, five participants attained scores in the unimpaired range (two were average), bringing into question the accuracy of pre-CA classifications and demonstrating the difficulty in assessing baseline function in the ICU setting in young, medically complex children. Also, coma resolved in three of the four who were comatose at hospital discharge (one scoring in the unimpaired range at 12 mo), illustrating the challenge of early neuroprognostication in this population.

Cognitive testing confirmed severe impairment in 12 of 16 (75%) of those less than 6 years old. All those greater than or equal to 6 years old were severely impaired (one received the lowest possible scores, seven were not tested due to lack of a functional means of communication). The developmental quotients helped to delineate the range of outcomes in this severely impaired group. However, although cognitive testing adds to our understanding of this group's outcome, its inclusion for similar subgroups in future trials may not be warranted, unless measures with a lower floor are used.

Strengths of this study include the prospective design, relatively large sample size compared with existing reports, broad pediatric age range, high follow-up rate, detailed CA characteristics, baseline assessment of function, and outcome measures assessing multiple domains of functioning (by both caregiver report and on-site objective assessment). This is a unique CA cohort, restricted to those with preexisting neurobehavioral impairment, a group under-represented in the literature. Given their clinical examinations after return of spontaneous circulation, they were at high risk for incremental acquired disability from hypoxic-ischemic brain injury. These results provide a framework for understanding the range of possible outcomes in this subset of children after CA, and although limited, represent the best data available at this time. However, results cannot be generalized to all pediatric CA survivors, especially those not comatose in the immediate 6-hour post-resuscitation period or other trial exclusion.

Limitations include possible inaccuracies in pre-CA assessment given the necessity to assess pre-CA functioning rapidly, during a time of crisis, often at young ages (< 2 yr old). This was a heterogeneous cohort, and with the modest sample size, it was not feasible to evaluate predictors of outcome (age, acute medical variables). It is unknown how preexisting deficits influenced likelihood of enrollment in the trials (from the perspectives both of treating physicians and of families). Data collection did not include some variables that might influence outcome (e.g., length of coma, seizure burden, neuroimaging, post-discharge medications, rehabilitation services, subsequent illness, and procedures).

CONCLUSIONS

In children with pre-CA neurobehavioral impairment who were comatose after CA, one-third survived. Survival was lower after IH-CA (but not OH-CA) when compared with those without pre-CA neurobehavioral impairment. Significant declines in neurobehavioral function occurred in 12-month survivors, more so after OH-CA than IH-CA. However, function remained unchanged or improved in 43%. Although the magnitude and frequency of change were different for those with, compared with those without pre-CA neurobehavioral impairment, the main results (categorical outcomes, treatment, and group effect) were similar. Results show that this group's inclusion in THAPCA was both feasible and informative when change from pre-CA functioning was used to evaluate outcomes. However, detecting decline in functioning was challenging, supporting the decision to include them in THAPCA's secondary but not primary outcomes.

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