Targeted Temperature Management After Pediatric Cardiac Arrest Due To Drowning: Outcomes and Complications*

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***See also p. 789.**

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Additional, in part, support from the following research networks: Pediatric Emergency Care Applied Research Network (PECARN) from cooperative agreements U03MC00001, U03MC00003, U03MC00006, U03MC00007, and U03MC00008; and the Collaborative Pediatric Critical Care Research Network (CPCCRN) from cooperative agreements U10HD500009, U10HD050096, U10HD049981, U10HD049945, U10HD049983, U10HD050012, and U01HD049934. Site support from P30HD040677, UL1TR000003UL1, RR 024986, and UL1 TR 000433.

This work is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or National Institutes of Health. Our work is important because it represents the first multicenter randomized study of therapeutic hypothermia and therapeutic normothermia for pediatric drowning. Mortality and functional outcomes at 1 year follow up, as well as, prospectively measured adverse event details are described. This report provides new and incremental information about outcomes of pediatric cardiac arrest due to drowning.

Supported by the National Heart, Lung, and Blood Institute (NHLBI) grants HL094345 (to Dr. Moler) and HL094339 (to Dr. Dean). Support, in part, received from the following federal planning grants contributed to the planning of the THAPCA Trials: HD044955 and HD050531 (to Dr. Moler). Dr. Moler received support for article research from the National Institutes of Health (NIH). His institution received funding from the NHLBI. Dr. Hutchison received support for article research from the NIH. His institution received funding from the NIH. Dr. Nadkarni received support for article research from the NIH and disclosed off-label product use (Therapeutic Hypothermia for the indication post-cardiac arrest is off label). His institution received funding from NICHD (NIH) U01 for THAPCA. Dr. Silverstein received support for article research from the NIH and received funding from the March of Dimes Scientific Advisory Board. His institution received funding from the Health) U01 for THAPCA NIH-NHLBI. Dr. Meert received support for article research from the NIH and disclosed other support (NIH grant). Her institution received funding from the NIH. Dr. Holubkov received other support (Additional Current: Physicians Committee for Responsible Medicine [Biostatistical Consultation] and the American Burn Association [DSMB Membership]); received support for article research from the NIH; and received funding from Pfizer (DSMB Memberships), St. Jude Medical (Biostatistical Consultation), and Fibrocell (DSMB Membership). His institution received funding from the NIH/NHLBI. Dr. Page received support for article research from the NIH. His institution received funding from the NIH. Dr. Sliminess received support for article research from the NIH, received funding from the University of California-Davis(for DSMB membership work), the American Academy of Clinical Neuropsychology (for lectures at annual meetings), and the American Psychological Association (for work as Associate Editor for Rehabilitation Psychology). Her institution received funding from the University of Michigan via NHLBI. Dr. Christensen received support for article research from the NIH. His institution received funding (Grant to THAPCA from NHLBI). Dr. Dean received support for article research from the NIH. His institution received funding from the NIH.

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DOI: 10.1097/PCC.0000000000000763

Objective: To describe outcomes and complications in the drowning subgroup from the Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital trial.

Design: Exploratory post hoc cohort analysis.

Setting: Twenty-four PICUs.

Patients: Pediatric drowning cases.

Interventions: Therapeutic hypothermia versus therapeutic normothermia.

Measurements and Main Results: An exploratory study of pediatric drowning from the Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital trial was conducted. Comatose patients aged more than 2 days and less than 18 years were randomized up to 6 hours following return-of-circulation to hypothermia ($n = 46$) or normothermia ($n = 28$). Outcomes assessed included 12-month survival with a Vineland Adaptive Behavior Scale score of greater than or equal to 70, 1-year survival rate, change in Vineland Adaptive Behavior Scale-II score from prearrest to 12 months,

and select safety measures. Seventy-four drowning cases were randomized. In patients with prearrest Vineland Adaptive Behavior Scale-II greater than or equal to 70 ($n = 65$), there was no difference in 12-month survival with Vineland Adaptive Behavior Scale-II score of greater than or equal to 70 between hypothermia and normothermia groups (29% vs 17%; relative risk, 1.74; 95% CI, 0.61–4.95; $p = 0.27$). Among all evaluable patients ($n = 68$), the Vineland Adaptive Behavior Scale-II score change from baseline to 12 months did not differ ($p = 0.46$), and 1-year survival was similar (49% hypothermia vs 42%, normothermia; relative risk, 1.16; 95% CI, 0.68–1.99; $p = 0.58$). Hypothermia was associated with a higher prevalence of positive bacterial culture (any blood, urine, or respiratory sample; 67% vs 43%; $p = 0.04$); however, the rate per 100 days at risk did not differ (11.1 vs 8.4; $p = 0.46$). Cumulative incidence of blood product use, serious arrhythmias, and 28-day mortality were not different. Among patients with cardiopulmonary resuscitation durations more than 30 minutes or epinephrine doses greater than 4, none had favorable Pediatric Cerebral Performance Category outcomes (≤ 3).

Conclusions: In comatose survivors of out-of-hospital pediatric cardiac arrest due to drowning, hypothermia did not result in a statistically significant benefit in survival with good functional outcome or mortality at 1 year, as compared with normothermia. High risk of culture-proven bacterial infection was observed in both groups. (*Pediatr Crit Care Med* 2016; 17:712–720)

Key Words: cardiac arrest; clinical trial; drowning; functional outcome; mortality; pediatric; therapeutic hypothermia

Out-of-hospital cardiac arrest (OHCA) in children commonly results in death or poor long-term functional outcome in survivors (1–3). In 2002, two trials in adults reported that therapeutic hypothermia (hypothermia) improved neurological outcomes in comatose survivors following OHCA with a shockable rhythm (4, 5). A more recent trial in adults reported that hypothermia (targeted temperature management [TTM], 33°C) did not improve outcomes compared to actively maintained therapeutic normothermia (normothermia) (TTM-36°C) (6). The fundamental difference between the trials was the normothermia comparison group, which was an active intervention to prevent fever (4–6). Recently, the first trial of TTM after pediatric cardiac arrest was reported. Hypothermia (TTM-33°C) was not superior to normothermia (TTM-36.8°C) for survival with good neurological outcome or mortality (7). Newly published 2015 international resuscitation guidelines now recommend either hypothermia or normothermia for comatose adults and children with OHCA (8, 9).

Drowning is an important cause of OHCA in children and results in approximately 1,100 pediatric deaths in the United States annually (10). One multicenter cohort study of children who incurred OHCA with return of circulation reported nearly one-third of cases attributable to drowning (43/138, 31%); drowning outcomes were better than outcomes in nondrowning cases (3). Yet, a recent Dutch retrospective cohort study reported no survivors of drowning with good functional outcome 1 year later (defined as Pediatric Cerebral Performance Category [PCPC] Scale score of ≤ 3) if temperature was less than 34°C on hospital presentation and more than 30 minutes of cardiopulmonary resuscitation (CPR) was required (11).

No randomized interventional clinical trials in children resuscitated after OHCA secondary to drowning have been published; information about interventions to improve outcome is limited to case reports or other observational studies (12–17). Recent expert reviews, however, cite hypothermia post arrest as a potentially beneficial therapy (18, 19). Additionally, international resuscitation guidelines for hypothermic comatose postarrest drowning patients recommend rewarming to and maintaining temperature in a hypothermia range (32–34°C) (20). Reliance on case series reports may be misleading due to reporting and publication bias or chance observation. Therefore, larger multicenter prospective investigations with longer follow-up would significantly augment existing knowledge.

Sporadic case reports of ice-water drowning with prolonged cardiac arrest durations have described more favorable neurological outcomes than anticipated with (12–16) or without extracorporeal membrane oxygenation treatment (17). Implementation of hypothermia after OHCA due to drowning was investigated over 25 years ago; in this case series, no clinical benefit was described and major complications of hypothermia were neutropenia and severe septicemia (21). The goal temperature range described (30–33°C) was lower than in more recently conducted neonatal (22), adult (4–6), and pediatric (7) TTM trials; this may have contributed to the complications reported. Analysis of data from a recent neonatal encephalopathy hypothermia trial reported a trend of higher mortality with TTM-32°C than with TTM-33.5°C (23).

We conducted an exploratory subgroup analysis focused on the subgroup of drowning cases from our recently published Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) Trial (7). First, we examined the efficacy and safety of hypothermia (TTM-33°C) versus normothermia (TTM-36.8°C) for the drowning cohort for the following outcomes: 1) survival with favorable 12-month outcome, defined as a Vineland Adaptive Behavior Scale, second edition (VABS-II) score of greater than or equal to 70; 2) change in VABS-II score from prearrest to 12 months; 3) survival at 12 months; and 4) select prospectively monitored adverse outcomes (blood product use, serious arrhythmias, and culture proven infection). We additionally examined 5) outcomes in the drowning cases with CPR greater than 30 minutes to determine whether our North American experience was similar to a recent Dutch report that found no survivors with good functional outcome (defined as PCPC ≤ 3) if CPR duration was over 30 minutes (11). This report provides new and incremental information about outcomes of pediatric cardiac arrest due to drowning treated at North American ICUs.

MATERIALS AND METHODS

Overview and Study Design

The details of planning the THAPCA trials were published (24–26). The findings of the THAPCA-OH trial were recently reported, and protocol details were provided in a designated section of the Supplementary Appendix in ref. (7). This was a National Heart, Lung, and Blood Institute–funded randomized clinical trial, conducted in PICUs at 36 children's hospitals in the United States and Canada. The institutional review boards of all participating sites and the data-coordinating center (DCC) approved the protocol and informed consent documents. Site research coordinators collected all data, and statisticians at the DCC performed all analyses for both the initial trial results and the current report.

Patient Population and Randomization

Children older than 48 hours and younger than 18 years who sustained OHCA, required chest compressions for at least 2 minutes, and remained comatose and dependent on mechanical ventilation after return of circulation, met the original inclusion criteria. The only additional requirement in the current report was that the etiology of the cardiac arrest was drowning. Major exclusion criteria were inability to randomize within 6 hours of return of circulation, a score of 5 or 6 on the Glasgow Coma Scale (GCS) motor response subscale (scores range from 1 to 6, lower scores indicate worse function), lack of commitment to aggressive care, association with major trauma, and drowning in ice-covered water; all exclusion criteria are listed in the trial report in the Supplementary Appendix in ref. (7). Written informed consent from a parent or legal guardian was required. Eligible subjects were randomized 1:1 to hypothermia or normothermia, using permuted blocks stratified by clinical center and age (< 2, 2–11, and 12 yr old or older).

Interventions

TTM was actively maintained for 120 hours in both groups. Children assigned to hypothermia were pharmacologically paralyzed, sedated, and cooled (or warmed if indicated) by surface cooling using a Blanketrol III cooling unit (Cincinnati SubZero, Sharonville, OH) with mattresses applied anteriorly and posteriorly, to achieve and maintain 33°C (32–34°C) core temperature for 48 hours. They were rewarmed over 16 hours or longer to target temperature 36.8°C (36–37.5°C); this temperature was actively maintained throughout the remaining 120-hour intervention period. Children randomized to normothermia received identical care except core temperature was actively maintained at 36.8°C (36–37.5°C) for 120 hours with the Blanketrol-III. Dual central temperature monitoring (esophageal, rectal, or bladder) and a servocontrol mode were used. The probe connected to the Blanketrol was designated primary; the other was connected to the bedside monitor for backup. Clinical teams determined all other aspects of clinical care.

Outcomes

The primary outcome of THAPCA-OH trial was survival with favorable neurobehavioral outcome at 12-month follow-up, defined as an age-corrected VABS-II standard score of greater than or equal to 70 (27). The VABS-II has an age-corrected mean of 100 (SD, 15); higher scores indicate better performance. VABS-II data were collected centrally (Kennedy-Krieger Institute, Baltimore, MD) via telephone by a trained interviewer blinded to treatment assignment. As prespecified in the protocol, enrolled children whose reported prearrest VABS-II scores were less than 70 (based on data from formal parent interview at each site within 24 hr of randomization) were not included in the primary efficacy analysis. Subjects without a baseline VABS-II were eligible for the primary analysis if both baseline Pediatric Overall Performance Category (POPC) and PCPC scores (28) were in the normal or mild disability category (29). POPC and PCPC scores range from 1 to 6, with lower scores representing less disability; subjects with scores of 1 or 2 on both scales were eligible for the primary analysis. POPC and PCPC were scored at baseline and at 12 months.

Secondary efficacy outcomes were 12-month survival and change in VABS-II score from prearrest baseline to 12-month score; deceased patients and those with the lowest possible VABS-II score were assigned the worst possible outcomes. Safety outcomes included the prevalences of blood product use, infection, and serious arrhythmias through 7-day and 28-day mortality. Complete blood counts were performed daily with values within 12 hours of 0, 24, 48, 72, 96, and 120 hours described.

Statistical Analyses

The efficacy analysis for the primary outcome used a prespecified modified intention-to-treat approach, excluding children with poor prearrest neurobehavioral function. Secondary efficacy outcomes were analyzed among all children. Safety analyses were done by treatment received among treated patients only. The primary outcome and 12-month mortality were compared between assigned treatment groups using a Cochran-Mantel-Haenszel test stratified by categorized age. Change in VABS-II was analyzed using van Elteren's modification of the Mann-Whitney *U* test (30), stratifying by categorized age, treating death as the worst outcome and treating the lowest possible VABS-II score at 1 year as the second-worst outcome. The probability of 1-year survival was evaluated by comparing survival curves between groups using a log-rank test stratified by age category. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). For these exploratory analyses, an α level of 0.05 was used with two-sided tests conducted. There was no adjustment for multiple statistical testing and no predetermined power calculation for the drowning cohort.

RESULTS

Population

Between September 1, 2009, and December 31, 2012, 74 drowning cases from 24 of the 36 sites were randomized; 46 were assigned to hypothermia (TTM-33°C) and 28 to normothermia (TTM-36.8°C); two cases in the hypothermia group and one in the normothermia group were ineligible for the primary outcome analysis. At 12 months, vital status was unknown in three in hypothermia and two in normothermia cases; one

TABLE 1. Baseline Characteristics Before Randomization

Characteristic	Overall *n*	Hypothermia Group (*n* = 46)	Normothermia Group (*n* = 28)
Demographic characteristics			
Age (yr), median (Q1–Q3)	74	2.4 (1.5–5.9)	3.6 (1.9–8.2)
Male sex, *n* (%)	74	28 (61)	22 (79)
Medical history, *n* (%)			
No preexisting medical condition	74	32 (70)	22 (79)
Characteristics of the cardiac arrest			
Bystander witnessed cardiac arrest, *n*/total *n* (%)	71	8/44 (18)	4/27 (15)
Bystander performed CPR, *n*/total *n* (%)	71	40/46 (87)	18/25 (72)
Initial rhythm noted by EMS or hospital, *n* (%)	74		
Asystole		29 (63)	19 (68)
Bradycardia		2 (4)	0 (0)
Pulseless electrical activity		7 (15)	4 (14)
Ventricular fibrillation or tachycardia		0 (0)	2 (7)
Unknown		8 (17)	3 (11)
Duration of CPR (min), median (Q1–Q3)	42	21.0 (14.0–34.0)	32.0 (16.0–55.0)
Estimated duration of CPR (min), median (Q1–Q3)	69	25.0 (14.0–35.0)	32.0 (17.5–55.0)
First hospital patient arrived at was the study hospital, *n* (%)	74	17 (37)	9 (32)
Chest compressions still required at time of arrival at the first hospital, *n*/total *n* (%)	71	23/44 (52)	17/27 (63)
No. of doses of epinephrine, median (Q1–Q3)			
Administered by EMS	70	1.0 (0.0–4.0)	1.0 (0.0–3.0)
Administered at hospital	74	1.0 (0.0–3.0)	2.0 (0.0–4.0)
All doses administered by EMS and at hospital	70	4.0 (1.0–6.0)	3.0 (2.0–5.0)
Baseline Vineland Adaptive Behavior Scale, second edition-II score, mean ± SD	67	98.2 ± 13.0	97.2 ± 19.8
Baseline Pediatric Cerebral Performance Category, *n* (%)	74		
Normal = 1		41 (89)	27 (96)
Mild disability = 2		3 (7)	0 (0)
Moderate disability = 3		2 (4)	0 (0)
Severe disability = 4		0 (0)	1 (4)

CPR = cardiopulmonary resuscitation, EMS emergency medical services.

normothermia group survivor did not complete VABS-II testing. Thus, 65 drowning cases were evaluable for the primary outcome.

Baseline Characteristics and Temperature Intervention

Baseline characteristics (**Table 1**) included median age 2.9 years (interquartile range [IQR], 1.6–8.0 yr) with male gender 68% (50/74). Bystanders witnessed 17% (12/71) and performed CPR for 82% of CA (58/71). The initial rhythm was asystole in 65% (48/74) and ventricular fibrillation or ventricular tachycardia in only 3% (2/74). Estimated median CPR duration for 69 cases (with accurate start and stop times or estimated start or stop time) was 25.0 minutes (IQR, 15.0–35.0 min); in 42 of these cases with accurate start and stop times available, median CPR duration was 24.5 minutes (IQR, 15.0–35.0 min). CPR was ongoing at initial hospital arrival in 56% (40/71). The median number of epinephrine doses (total) was 3.5 (IQR, 1.0–5.0) (available in 70 cases). The two groups were similar with respect to other baseline information. The median time (hr) from return of circulation to treatment initiation was 5.8 (IQR, 5.1–6.7) in the hypothermia group and 5.7 (IQR, 5.0–6.3) in the normothermia group. No subjects received extracorporeal life support.

TABLE 2. Primary and Secondary Outcomes After Pediatric Cardiac Arrest Due to Drowning

Outcome	Overall *n*	Hypothermia Group	Normothermia Group	Risk Difference (95% CI)	Relative Risk (95% CI)	*P* value
Primary outcome						
Alive and VABS-II score ≥ 70 at 1 yr	65	12/41 (29%)	4/24 (17%)	12.6% (−7.8 to 33.0)	1.74 (0.61–4.95)	0.27[a]
Secondary outcomes						
Alive at 1 yr	69	21/43 (49%)	11/26 (42%)	6.5% (−17.6 to 30.7)	1.16 (0.68–1.99)	0.58[a]
1 yr change in VABS-II score from baseline	68	*n* = 43	*n* = 25			0.46[b]
Death, *n* (%)		22 (51)	15 (60)			
Lowest possible VABS-II score, *n* (%)		0 (0)	0 (0)			
VABS-II score decreased > 30 points, *n* (%)		8 (19)	4 (16)			
VABS-II score decreased 16–30 points, *n* (%)		3 (7)	1 (4)			
VABS-II score decreased no more than 15 points or improved, *n* (%)		10 (23)	5 (20)			

VABS-II = Vineland Adaptive Behavior Scale, second edition.

[a]*p* value reflects the Cochran-Mantel-Haenszel test, adjusted for age stratum.

[b]*p* value reflects the Mann-Whitney test based on the continuous change in VABS score, stratified by age category. Deceased patients and those with the lowest possible VABS score are assigned ranks of −2,000 and −1,000, respectively (i.e., the worst possible scores).

Outcomes

The proportion of survivors with VABS-II scores of greater than or equal to 70 at 12 months did not differ between groups (hypothermia and normothermia groups, 29% vs 17%; relative risk, 1.74; 95% CI, 0.61–4.95; $p = 0.27$) (**Table 2**). Change from baseline to 12-month VABS-II score also did not differ ($p = 0.46$). The proportion of cases with 12-month VABS-II scores within 15 points (1 SD) of their baselines was similar (hypothermia, 23%; normothermia, 20%; Table 2).

Twelve-month mortality was assessed for all randomized cases with known vital status (69/74; 93%). Survival did not differ (hypothermia, 49%; normothermia, 42%; relative risk, 1.16; 95% CI, 0.68–1.99; $p = 0.58$) (Table 2) nor did survival time differ (log-rank test, $p = 0.52$) (**Fig. 1**). **Table S1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A253) summarizes the primary causes of death, which were not statistically different between groups; brain death or withdrawal of technological support due to poor neurologic prognosis was reported in the majority of cases in both groups (91%, hypothermia; 73%, normothermia).

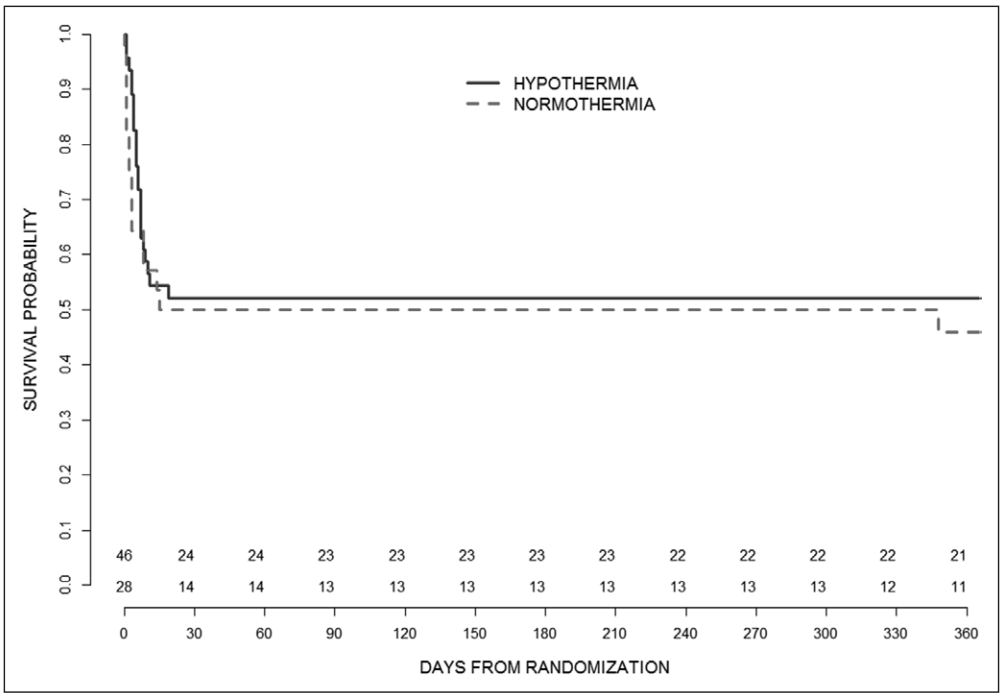

Figure 1. Survival curve though 365 d for therapeutic hypothermia and therapeutic normothermia groups.

Table 3 describes 12-month PCPC and VABS-II outcomes for all cases, overall, and grouped by treatment and estimated chest compression duration (≤ 30 or > 30 min). There were no survivors with PCPC less than or equal to 3 in either group among cases with CPR greater than 30 minutes. Overall, in the less than

TABLE 3. Twelve-Month Pediatric Cerebral Performance Category and Vineland Adaptive Behavior Scale, Second Edition Outcomes by Duration of Cardiopulmonary Resuscitation

	Estimated Duration of Cardiopulmonary Resuscitation		
Outcome	**≤ 30 min (*n* = 44)**	**> 30 min (*n* = 25)**	**Unknown (*n* = 5)**
12-mo Pediatric Cerebral Performance Category, *n* (%)			
Missing	5 (11)	0 (0)	1 (20)
Normal = 1	10 (23)	0 (0)	0 (0)
Mild disability = 2	2 (5)	0 (0)	0 (0)
Moderate disability = 3	3 (7)	0 (0)	0 (0)
Severe disability = 4	4 (9)	5 (20)	1 (20)
Coma or vegetative state = 5	3 (7)	3 (12)	0 (0)
Death = 6	17 (39)	17 (68)	3 (60)
12-mo Vineland Adaptive Behavior Scale, second edition			
n	22	8	1
Mean ± SD	80 ± 29	46 ± 15	65
Median (interquartile range)	91 (51–102)	41 (37–49)	65 (65–65)
Range	27–117	35–80	65–65

or equal to 30-minute CPR group, median VABS-II score was 91 (IQR, 51–102) compared with 41 (IQR, 37–49) for group with CPR greater than 30 minutes. There was one noteworthy discrepancy observed between the VABS-II and the PCPC classification of 1-year outcome in a single drowning survivor, who was categorized with a PCPC of 4 and VABS of 80. This child had neurologically based motor impairments and average communication and socialization skills. Although the correlation between PCPC and VABS is high (29), the VABS-II score is based on average functioning across several specific domains, whereas the PCPC category is based on overall level of functioning and assistance needed. **Table S2** (Supplemental Digital Content 1, http://links.lww.com/PCC/A253) depicts epinephrine dose received and outcomes. No 1-year survivors received more than 11 doses, and no survivors with favorable outcome (1-yr PCPC ≤ 3) received more than four doses. Similarly, no survivors with favorable outcome alternatively defined as 1-year PCPC of 1 or 2, or no change if baseline was greater than 2, received more than four epinephrine doses.

Safety

Table 4 summarizes the prevalence of prospectively monitored safety outcomes in all drowning cases. There was a trend for increased administration of blood products in the hypothermia group compared with the normothermia group (50 vs 29%; $p = 0.08$). The frequency of severe arrhythmias within 7 days of cardiac arrest was similar in both groups. Twenty-eight–day mortality was not different (hypothermia 48% vs normothermia 50%; $p = 0.86$). Culture-proven bacterial infection from blood, respiratory, and urine sites was more frequent in the hypothermia group (67% vs 43%; $p = 0.04$). A broad range of Gram-positive and Gram-negative bacteria was cultured (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/PCC/A253).

Table S4 (Supplemental Digital Content 1, http://links.lww.com/PCC/A253) provides blood count data. Statistically significant differences were observed with the following: hemoglobin was lower in the normothermia group at 24 and 48 hours; platelet counts were lower at 72, 96, and 120 hours for the hypothermia group; WBC counts were lower at 48 hours in the hypothermia group.

DISCUSSION

We conducted this exploratory subgroup study of pediatric drowning and TTM because there are no randomized multicenter interventional study publications on this condition and because the drowning group represents a relatively homogenous group making up a relatively large proportion of cases in the THAPCA-OH trial population. In addition, better outcomes have been reported among drowning cases compared with other causes of pediatric OHCA after adjusting for severity (3). As in the full THAPCA-OH trial (7), we found no difference for the drowning cohort in survival with favorable neurobehavioral outcome at 12 months between hypothermia and normothermia groups. Change in VABS-II score from baseline to 1 year or proportion of children with VABS-II scores within 15 points of their baselines (23 vs 20%) also did not differ between groups. One-year all-cause mortality rates and corresponding survival analysis were similar. Culture-positive bacterial infection from combined sources of blood, urine, and respiratory was high in both groups and more common in the

TABLE 4. Safety Outcomes Within 7 Days After Randomization and 28-Day Mortality

Outcome	Hypothermia Group (*n* = 46)	Normothermia Group (*n* = 28)	*p*[a]
Blood-product use, *n* (%)			
Overall (any type)	23 (50)	8 (29)	0.08
Cryoprecipitate	1 (2)	0 (0)	0.62
Fresh frozen plasma	15 (33)	5 (18)	0.18
Packed red blood cells/whole blood	15 (33)	4 (14)	0.09
Platelets	3 (7)	0 (0)	0.23
Arrhythmias, *n* (%)			
Any serious arrhythmias	3 (7)	3 (11)	0.55
Asystole	1 (2)	3 (11)	0.17
Atrial (supraventricular tachycardia, atrial flutter, junctional ectopic tachycardia)	1 (2)	0 (0)	0.62
Pulseless electrical activity	1 (2)	0 (0)	0.62
Ventricular (sustained ventricular tachycardia > 30 s, ventricular fibrillation, Torsades)	0 (0)	0 (0)	1.00
Other	1 (2)	1 (4)	0.76
Culture-proven infections[b]			
Overall (any), *n* (%)	31 (67)	12 (43)	0.04
Blood, *n* (%)	3 (7)	2 (7)	0.91
Respiratory, *n* (%)	23 (50)	9 (32)	0.14
Urine, *n* (%)	6 (13)	2 (7)	0.47
Total no. of infections			
Overall	36	14	
Blood	3	2	
Respiratory	26	10	
Urine	7	2	
No. of days at risk	323	166	
Rate (95% CI) of infections per 100 d at risk[c]			
Overall	11.1 (7.8–15.4)	8.4 (4.6–14.2)	0.46[c]
Blood	0.9 (0.2–2.7)	1.2 (0.1–4.4)	1.00
Respiratory	8.0 (5.3–11.8)	6.0 (2.9–11.1)	0.49
Urine	2.2 (0.9–4.5)	1.2 (0.1–4.4)	0.73
All cause 28-d mortality, *n* (%)	22 (48)	14 (50)	0.86

[a]*p* values for all comparisons, except where noted, are two-sided mid *p* values, based on an exact likelihood ratio test.

[b]For completeness: one eye culture with stenotrophomonas maltophilia and staphylococcus coagulase negative (excluded); respiratory culture isolation of adenovirus; parainfluenza excluded; one blood culture with diphtheroids (excluded).

[c]CIs are exact two-sided 95% CIs, and *p* values are based on an exact test of homogeneity of event rates between the hypothermia arm and the normothermia arm, assuming event data follow Poisson distributions.

hypothermia than in the normothermia group; this trend has also been reported in adult OH-CA survivors (25–27).

The current report describes the largest cohort of pediatric drowning cases randomized for any intervention to date, and it is the first multicenter pediatric drowning study that evaluated TTM and that included assessments of function both at baseline and at 1 year later, using standardized neurobehavioral measures (7). The study is limited by relatively small sample size (about one-fourth of cases from the THAPCA-OH trial) and limited power to detect all but very large effect sizes.

Nonetheless, this information will inform planning of future investigations and potentially contribute to future meta-analysis of pediatric drowning outcomes.

It should be noted that our results cannot be generalized to all drowning cases, as the THAPCA-OH trial had strict inclusion and exclusion criteria. For example, patients with initial GCS motor score of greater than or equal to 5 (localizing or withdrawing to touch), indicating less severe neurologic injury were excluded. In addition, cases were excluded if the clinical teams determined patients were too hemodynamically unstable or implemented limitations to intensive care support in the first 6 hours after return of circulation.

Another limitation of this analysis shared by other studies is the difficulty inherent in distinguishing infection from colonization for the bacterial respiratory culture results. Chest x-rays of drowning patients often demonstrate pulmonary aspiration infiltrates at hospital presentation, and because TTM in both groups prevented fever, this intervention made it difficult to diagnose pneumonia. Although hypothermia was associated with higher overall risk (combined blood, respiratory, and urine) culture-proven bacterial infections, there was also a very high positive culture risk in the normothermia group. High risk of pneumonia after adult OHCA has been reported (6, 31–33). In one large post-OHCA adult cohort study, high risk of pneumonia (48%), but low risk of sepsis (4%), was described in cases treated with hypothermia (33); in a recent large adult clinical trial of TTM the risk of pneumonia was 52% (TTM-33°C) versus 46% (TTM -36°C) and risk of sepsis 10% in both TTM groups (6). Prophylaxis or early antibiotic therapy for positive cultures should be considered. The wide range of organisms isolated in our study (Table S2, Supplemental Digital Content 1, http://links.lww.com/PCC/A253) indicates broad-spectrum Gram-positive and Gram-negative antibiotic coverage would be needed if empiric treatment was utilized, a finding consistent with previous drowning reports (34, 35). An observational report of hypothermia from over 25 years ago described a high prevalence of severe sepsis (6/24 in the hypothermia group had blood stream infection) and neutropenia in pediatric drowning cases (21); however, the hypothermia intervention included both a lower targeted temperature goal and a longer duration of hypothermia. Recent advances in ICU care such as prevention bundles for catheter associated–blood stream infection may also have contributed to the lower risk (7%) of blood stream infection in both groups in the current era report (Table 3).

A recent retrospective Dutch cohort study of pediatric drowning cases with temperature of less than 34°C on hospital admission reported no survivors with favorable functional outcomes (defined as PCPC ≤ 3) if CPR duration was over 30 minutes (11). Similarly, in our drowning cohort, eight of 25 cases with CPR duration over 30 minutes survived, three in a persistent vegetative state (PCPC = 5) and five with severe disability (PCPC = 4). However, it should be noted that because only 25 (hypothermia [12] and normothermia [13]) drowning cases had CPR durations estimated over 30 minutes, the upper limit for the true population good outcome rate (using an exact 95% CI) within this subgroup is 14%, with zero good outcomes observed. Our trial did not collect temperature at the time of arrival to the first hospital; however, based on other reports, the majority of drowning cases are hypothermic on arrival to the hospital. One large cohort study with 1,094 drowning cases reported duration of submersion, but not water temperature to be associated with drowning outcome (36).

Unanswered questions remain concerning the potential role of TTM for pediatric OHCA due to drowning. Alternative durations of TTM (longer or shorter), different depths of TTM control (higher or lower), and a different therapeutic window for initiating hypothermia (shorter) are modifications that might be considered for future study (7, 23). Modification of inclusion and exclusion criteria such as inclusion of cases with GCS motor score equal to 5 and exclusion of cases with greater than 30 minutes of CPR might be considered. Combining TTM with neuroprotective agents might also be considered in future pediatric cardiac arrest drowning trials.

CONCLUSION

For comatose survivors of pediatric OHCA due to drowning from the THAPCA-OH trial, hypothermia could not be shown to result in a statistically significant benefit with respect to survival with good functional outcome at 1 year when compared with normothermia. Mortality risk at 28 days and 12 months also did not differ between treatment groups. The hypothermia group had an overall higher proportion with positive bacterial cultures (any respiratory, blood, and urine) compared with normothermia; however, both groups had high risk of positive cultures. For both groups, all 12-month survivors who had undergone more than 30 minutes of chest compressions had poor functional outcomes (PCPC ≥ 4).

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