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Therapeutic hypothermia after paediatric cardiac arrest

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INTRODUCTION

Therapeutic hypothermia (hypothermia) as compared to therapeutic normothermia (normothermia) for treatment of comatose children resuscitated after out-of-hospital or in-hospital cardiac arrest did not confer a significant benefit in survival with favourable functional outcome in two independent, parallel trials which utilized identical study protocols(1,2). Current paediatric guidelines recommend either hypothermia or normothermia for target temperature management (TTM)(3). However, since effect sizes tested were in the range of 10 to 20 percent, uncertainty persists regarding optimal temperature management.

In the broad paediatric age range, there are multiple differences between cardiac arrests occurring in the out-of-hospital versus in-hospital setting including patient demographics, underlying pre-existing pathology, aetiology of cardiac arrest, response times and resuscitative skills of the initial responders, and survival rates (4). These differences informed a decision by the THAPCA trials investigators to enrol patients into two separate independent parallel clinical trials (ClinicalTrials.gov NCT00880087 and NCT00878644). However, a major challenge in paediatric cardiac arrest trials is recruitment of sufficiently large sample sizes to detect small clinically significant differences(5). As the underlying mechanism for potential benefit from hypothermia after a hypoxic-ischemic insult is similar in both paediatric populations, the THAPCA trial investigators proposed a secondary analysis of the comparative efficacy and safety of the two temperature interventions in the combined population of out-of-hospital and in-hospital cardiac arrest study cohorts. We report here the results of the pooled data analysis from these two trials which used identical protocols.

METHODOLOGY

Design

The two THAPCA trials were conducted in paediatric intensive care units (ICUs) at 41 enrolling children's hospitals in the United States, Canada, and United Kingdom. The rationale, study design, outcome selection process, protocol summary, 12-month pilot vanguard phase and individual trial outcomes were previously published (6-8). Funding for both trials was from the National Heart, Lung, and Blood Institute (NHLBI). The trial protocols differed only in the inclusion criteria definition of out-of-hospital and in-hospital cardiac arrest(1,2). The institutional review boards of all participating sites and the data-coordinating centre approved the protocol and informed consent documents. Site research coordinators collected all data, and statisticians at the data-coordinating centre (University of Utah) performed all analyses. Site training, data management and site monitoring were described in the Supplementary Appendix of each trial report(1,2). All site investigators vouched for their submitted data. The current pooled study was approved by the THAPCA executive committee prior to analysis of either of the THAPCA trials.

Patient Population

Children ≥48 hours and <18 years old who sustained cardiac arrest, required chest compressions for ≥ two minutes, and required mechanical ventilation after return of circulation, met inclusion criteria. Major exclusion criteria were scores of 5 or 6 on the Glasgow Coma Scale motor response subscale (scores range from 1 to 6, lower scores indicate worse function), inability to randomize within 6 hours of return of circulation, active and refractory severe bleeding, pre-existing illness with life expectancy less than 12 months, and lack of commitment to aggressive care. Full exclusion criteria lists were provided in the Supplementary Appendix of the two trial reports(1,2). Written informed consent from a parent or legal guardian was required.

Randomization and Intervention

Eligible patients were randomized to hypothermia or normothermia in a 1:1 ratio using permuted blocks stratified by clinical centre and age (younger than 2 years, 2 to 11 years, and 12 years or older).

Targeted temperature management (TTM) was actively maintained for 120 hours in both groups, as previously described(1,2). Participants assigned to hypothermia were pharmacologically paralyzed, sedated and cooled (or warmed if indicated) by surface cooling using a Blanketrol III cooling unit (Cincinnati SubZero, Cincinnati) with mattresses applied anteriorly and posteriorly, to achieve and maintain 33°C (range 32-34°C) core temperature for 48 hours. They were rewarmed over 16 hours or longer to target temperature 36.8°C (range 36-37.5°C) which was actively maintained throughout the remainder of the 120 hour intervention period. Patients randomized to normothermia received identical care except core temperature was actively maintained at 36.8°C (range 36-37.5°C) for 120 hours with the cooling unit. Dual central temperature monitoring (oesophageal, rectal, or bladder) and a servo-control mode were used. For patients supported with extracorporeal membrane oxygenation (ECMO) at the time of randomization or later, temperature was controlled with ECMO using a single central temperature monitor. All other aspects of care were determined by clinical teams.

Outcomes

The primary outcome was survival with favourable neurobehavioral outcome at 12 month follow-up, defined as an age-corrected standard score ≥70 on the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II)(9). The VABS-II has an age-corrected mean score of 100 (standard deviation, 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 pre-specified in the protocol, enrolled children with pre-arrest VABS-II scores below 70 (based on data from caregiver questionnaire completed at each site within 24 hours of randomization) were excluded only from the primary efficacy analysis. Patients with no baseline VABS-II available were considered eligible for the primary analysis if their baseline Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores were in normal or mild disability categories(10,11). Scores on these scales range from 1 to 6, with lower scores representing less disability; patients with scores of 1 or 2 on both scales were eligible for the primary analysis.

Secondary outcomes were change in neurobehavioral function, measured as the difference from pre-arrest baseline to 12 month measurement on the VABS-II (assigning deceased cases and those with

lowest possible VABS-II scores worst possible outcomes, regardless of baseline function) and survival at 12 months. Safety outcomes included the incidences of blood product use, infection, and serious arrhythmias through seven days, and 28-day mortality. The outcome assessment methodology was previously described(1,2).

Statistical Analysis

Individual patient data from both primary trial datasets were combined. Identical definitions, coding, reference units and data collection processes were used for each trial enabling combination without loss of data items. The efficacy analysis for the primary outcome was performed using a pre-specified modified intention-to-treat approach in both trials, excluding children with poor pre-arrest neurobehavioral function. Secondary efficacy outcomes were analysed among all children. Safety analyses were done by treatment received. The primary outcome and 12 month mortality were compared between assigned treatment groups using a Cochran-Mantel-Haenszel test stratified by categorized age and study. Change in VABS-II was analysed using van Elteren's modification of the Mann-Whitney test (12), stratifying by categorized age and study, treating death as the worst outcome and the lowest possible VABS-II score as the second-worst outcome. For this exploratory investigation, significance was declared at the 0.05 for all tests. The probability of survival to one year was evaluated by comparing survival curves between arms using a log-rank test stratified by age category. Univariate analysis of prognostic risk factors for survival independent of treatment group were analysed. Multivariable analysis for prognostic factors for neurobehavioral outcome have been presented previously for each trial(13,14). Analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Cohort

Both trials commenced on September 1, 2009 with THAPCA-OH patients enrolled through December 31, 2012 at 36 centres in USA and Canada (2 did not recruit) and THAPCA-IH patients enrolled until February 27, 2015 at 37 sites in the USA, Canada and UK (9 sites did not enrol). Forty-seven centres

in total participated in at least one of the THAPCA trials, with 6 centres not randomizing at least one case. The full CONSORT Diagram is described in Appendix Fig 1. A total of 4146 patients met inclusion criteria and were screened; 1221 had no trial exclusion criteria and were eligible for enrolment; and 624 were enrolled, 321 randomized to hypothermia and 303 to normothermia. Eight patients, who were assigned to hypothermia and three normothermia, did not receive an intervention and one normothermia patient received hypothermia therapy. Five hundred and seventeen patients had VABS-II scores ≥70 at baseline, prior to their cardiac arrest, and were eligible for the primary outcome assessment.

The baseline characteristics of the two temperature treatment groups were similar (Table 1). Overall median age was 1.5 years IQR [0.3, 7.1] with 63% male; 71% had one or more pre-existing medical condition most frequent being cardiac, lung or airway, and neurological conditions. Thirty percent (190/624) had a primary cardiac aetiology for their arrest, 9% (57/624) presented with a shockable rhythm (ventricular fibrillation or ventricular tachycardia); and the median estimated duration of chest compressions was 25 minutes IQR [12, 42.5]. Time from return of spontaneous circulation after cardiac arrest to target temperature following randomization for hypothermia group was Median 6.9 hours [Interquartile range (IQR) 5.6 to 8.8] and normothermia group 6.4 hours [IQR 5.3 to 8.4].

Outcomes

The proportion of survivors with the primary outcome VABS-II score ≥70 at 12 months was not significantly different between those treated with hypothermia (28%) compared to the normothermia intervention (26%); relative risk 1.08; 95% confidence interval [CI] 0.81 to 1.42; p=0.61. In patients included in the primary analysis who died or had a profound (VABS-II <45 or lowest) or moderate to severe disability (VABS-ll 45-69), there was also no significant difference in proportion of patients treated with either therapy (p=0.4) (Table 2). The secondary outcome of one year change in VABS-ll score from baseline score did not differ between groups (p=0.20); nor did the proportion in whom the VABS-ll score decreased by no more than 15 points (1 standard deviation) or improve differ (hypothermia 22% versus normothermia 21%) (Table 2).

Survival at 12 months for 614 patients, whose outcome status was known, did not differ between groups (hypothermia 44% vs. normothermia 38%; relative risk 1.15; 95% CI 0.95 to 1.38; p=0.15) (Table 2).

Survival duration was longer for patients receiving hypothermia; (Figure 1a, p=0.045). Sensitivity analysis revealed that this difference was due to the greater number of deaths occurring in the normothermia groupbetween days 0 to 3 (Figure 1b, p=0.91; Supplemental Figure 2, p=0.003). Specifically, a greater number of deaths occurred on day 0 in the normothermia group (19 versus 5) and the majority (12/19) were due to cardiovascular failure/futility (Table 3). By 12 months, the proportions of deaths by individual causes were similar for patients treated with hypothermia and normothermia. The majority of deaths were attributed to brain death (24.6% versus 24.9%), withdrawal of medical support in view of poor neurological prognosis (35.8 versus 31.4%), or cardiovascular failure/futility (21.2% versus 24.9%) (Table 3).

Prognostic factors for survival and for survival at 12 months with VABS-II ≥70 were analysed (Table 4). A cardiac aetiology of cardiac arrest, initial rhythm of ventricular fibrillation or ventricular tachycardia, shorter duration of cardiopulmonary resuscitation, fewer epinephrine doses, and cardiac arrest occurrence during a weekday (versus weekend) and during the day (versus night) were each associated with improved survival, independent of treatment arm. Children whose cardiac arrest occurred in-hospital compared to out-of-hospital were almost twice as likely to survive (OR 1.79 [1.29, 2.49]) and three times as likely to survive with VABS-II ≥70 (OR 3.09, 95% CI [2.04, 4.69]) (see Supplemental Table 1).

Safety

Safety outcome data were available for 314 in the hypothermia group and 298 in the normothermia group. The incidences of blood-product use, infection, and serious arrhythmias within seven days did not differ between these groups; nor did 28 day mortality significantly differ [hypothermia, 146/314(46%) versus normothermia, 159/298(53%), p=0.10; (see Supplemental Table 2).

DISCUSSION

In this analysis of pooled data from two identically conducted targeted temperature management randomized clinical trials(1,2), there was no significant improvement in survival with favourable neurobehavioral outcome, defined as a VABS-II score ≥70 for hypothermia (28%) versus normothermia (26%) groups. Additionally, the best change from baseline outcome, defined as a VABS-II score reduction by no more than 15 points (1 SD) at one year, was similar for hypothermia (22%) and normothermia (21%) groups. Mortality at one year was not statistically different by temperature intervention, although earlier

deaths in the first three days of intervention were observed with normothermia. Hypothermia and normothermia groups had comparable safety profiles for blood product utilization, infection, serious cardiac arrhythmia and 28-day mortality.

We were able to perform a pooled randomized control trial (RCT) analysis, as opposed to an individual patient data (IPD) meta-analysis, because the RCT protocols were identical with respect to all elements including data definitions, collection and handling procedures, and primary and secondary outcomes. In addition, the trials were initiated concurrently and predominantly at sites that participated in both THAPCA trials, minimizing temporal and site-specific effects between trials. The justification for conducting separate trials stemmed from analysis of a pre-trial planning cohort study that found differences in the aetiology of arrest, initial cardiac arrest rhythm, resuscitation skills of initial responders and survival outcomes between paediatric out-of-hospital and in-hospital cardiac arrest populations(4,15,16). In fact, the substantial difference in proportion of favourable outcomes between the IH and OH cohorts provides support for the decision to conduct separate trials in these two paediatric populations.

The current investigation was planned and approved by the trial executive committee prior to completion of either trial. By combining the two trial datasets in the current investigation, we were able to further explore the impact of hypothermia versus normothermia to ameliorate severe hypoxic-ischemic injury following paediatric cardiac arrest in a sample approximately twice the size of the original trials. However, in the pooled population as in the individual trials, there were no statistically significant differences for the primary or two secondary outcomes. The larger sample size gained by combining the two trials leads to more precise confidence intervals for treatment effect than in each individual trial, more conclusively ruling out even moderate benefits of hypothermia.

In this study, both treatment arms received 120 hours of active temperature control, to prevent fever (temperature >37.5°C), using surface temperature control devices, pharmacological sedation and neuromuscular blocking medication as required. Our findings are similar to a large adult trial of targeted temperature management (TTM) of 33°C versus 36°C for 36 hours(17), which found no statistically significant difference in outcomes. However, neither the adult nor the paediatric trials compared active TTM with no active temperature control. Recent reports of actual practice temperature management of

adult cardiac arrest describe a change in TTM from 33°C to 36°C(18-20). This practice has been accompanied by trends in less active cooling, greater exposure to fever, and worse clinical outcomes(20). The reports suggest an actual practice 'belief' that fever prevention can be achieved without protocol guided sedation, neuromuscular blockage and servo regulated cooling devices. A large ongoing adult trial of hypothermia (33°C) versus standard care avoiding early fever (>37.8°C) management after cardiac arrest may provide needed information to address this critical question (ClinicalTrials.gov Identifier: NCT02908308).

Although there was no overall difference in survival at 12 months, we found a difference in time to death between hypothermia and normothermia treatment groups (Figure 1a; p=0.045)**.** This difference was explained by more early deaths in the normothermia group during days 0 through 3 (Figure 1c; p=0.003). There are at least two reasons for this observation. First, for day 0, increased deaths due to cardiac failure in the normothermia group was observed, although this trend largely balanced out by day 3 (Table 3). This suggests hypothermia may have been protective or provided additional inotropic effects for the myocardium in the early post arrest period. Early hypotension in the first 6 to 12 hours post cardiac arrest is associated with worse outcome in children comatose after cardiac arrest(21,22). Hypothermia has been reported to reduce inotropic or vasopressor requirement and reduce/rebalance myocardial work to oxygen demand(23). Following adult cardiac arrest, hypothermia increases systemic vascular resistance leading to reduced vasopressor use and lower oxygen consumption(24). In children, hypothermia has been reported as a useful salvage therapy for severe low cardiac output syndrome post congenital heart disease surgery(25). The second identifiable factor associated with hypothermia was lower numbers of deaths through day 3 that were attributable to brain death or to poor neurological prognosis [hypothermia 10% (31/321) versus normothermia 19% (57/303); p=0.001](Table 3). This likely reflected delays in neurological prognostic and brain death assessments in hypothermic patients until at least 24 hours after normothermia was achieved; this common practice stemmed from consideration that sedative drugs administered concurrently with hypothermia could have prolonged clearance and thereby confound clinical assessments(26).

There are limitations with the current study. As described previously, caregivers and research staff in the ICU were aware of treatment assignments of patients, although the primary outcome one year VABS-

II interview assessments were performed by individuals who were unaware of treatment group assignment(1,2). We could not rule out the possibility of earlier death or determination by clinical teams of futility in the normothermia group, as discussed above. Although planned prior to the completion of the two THAPCA trials, this pooled analysis was performed after publication of the two primary trials when the results were known to the investigators. A major strength of this study was that pooling of individual patient data analysis was possible due to identical protocols and data definitions. The larger sample size provided greater statistical power to show potential differences in neurobehavioral, mortality and safety outcomes. The inclusion and exclusion criteria selected patients with identical high risk of neurological morbidity and mortality. The final inclusion of 15% (624/4146) of initially screened patients may limit the generalization of the study findings to all paediatric cardiac arrest patients. However, the current pooled study included a more heterogeneous and generalizable population than did either individual trial. Inclusion of patients stratified with less severe injury, excluding the most severe hypoxic ischemic arrests (e.g. sudden infant death syndrome), or selecting a more homogeneous population (e.g. drowning) might allow more focused assessment of TTM efficacy. Unanswered questions remain regarding optimal evaluation of TTM. Future trials should consider different durations and depth of cooling (27-29), earlier onset of TTM, more precise patient stratification based on acute brain injury biomarkers, and adjunctive neuroprotective agents.

In conclusion, this larger pooled cohort of patients who were comatose after paediatric cardiac arrest from in-hospital or out-of-hospital locations, therapeutic hypothermia did not confer a statistically significant benefit in survival with a good functional outcome compared to therapeutic normothermia. Both hypothermia and normothermia active temperature interventions had similar severe adverse event profiles.

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REFERENCES

1. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. N Engl J Med 2015; 372:1898-908.

2. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. N Engl J Med. 2017; 376:318-329.

3. de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, et al. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132(18 Suppl 2):S526-42.

4. Moler FW, Meert K, Donaldson AE, Nadkarni V, Brilli RJ, Dalton HJ, et al. for the Pediatric Emergency Care Applied Research Network. In-hospital versus out-of-hospital pediatric cardiac arrest: A multicenter cohort study. Critical Care Med 2009; 37:2259-2267.

5. Kanthimathinathan HK, Scholefield BR. Dilemmas in undertaking research in paediatric intensive care. Archives of disease in childhood 2014;99:1043-9.

6. Moler FW, Silverstein FS, Meert KL, Clark AE, Holubkov R, Browning B, et al. Rationale, Timeline, Study Design and Protocol Overview of the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials. Pediatr Critical Care Med 2013; 14:e304-15.

7. Pemberton VL, Browning B, Webster A, Dean JM, and Moler FW. Therapeutic Hypothermia after Pediatric Cardiac Arrest Trial: The Vanguard Phase Experience and Implications for other Trials. Pediatr Critical Care Med 2013; 14:19-26.

8. Holubkov R, Clark AE, Moler FW, Slomine BS, Christensen JR, Silverstein FS, et al. Efficacy outcome selection in the Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) Trials. Pediatr Crit Care Med 2015; 16, 1-10.

9. Sparrow S, Cicchetti D, Balla D: Vineland Adaptive Behavior Scales. 2nd Edition. Minneapolis, MN: Pearson Assessment, 2005.

10. Fiser DH. Assessing the outcome of pediatric intensive care. J Pediatr 1992; 121:68-74.

11. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, and Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow- up

12. van Elteren PH. On the combination of independent two sample tests of Wilcoxon. Bulletin of the Institute of International Statistics 1960; 37:351–361.

13. Meert K, Telford R, Holubkov R, Slomine BS, Christensen JR, Berger J, et al. Cardiac Arrest Characteristics and their Association with Survival and Neurobehavioral Outcome after Pediatric Out-of-Hospital Cardiac Arrest. Pediatr Crit Care Med. 2016; 17(12):e543-e550.

14. Meert K, Telford R, Holubkov R, et al. Paediatric In-Hospital Cardiac Arrest: Factors associated with Survival and Neurobehavioural Outcome One Year Later. Resuscitation. 2018; 124:96-105.

15. Meert KL, Donaldson A, Nadkarni V, Tieves KS, Schleien CL, Brilli RJ, et al. Multicenter Cohort Study of In-Hospital Pediatric Cardiac Arrest. Pediatr Crit Care Med 2009; 10:544-553.

16. Moler FW, Donaldson AE, Meert K, Brilli RJ, Nadkarni V, Shaffner DH, et al. for the Pediatric Emergency Care Applied Research Network (PECARN). Multicenter Cohort Study of Out-of-Hospital Pediatric Cardiac Arrest. Crit Care Med 2011; 39:141-9.

17. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369:2197-206.

18. Deye N, Vincent F, Michel P, Ehrmann S, da Silva D, Piagnerelli M, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. Ann Intensive Care 2016; 6:4.

19. Nolan JP, Ferrando P, Soar J, Benger J, Thomas M, Harrison DA, Perkins GD. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. Crit Care 2016; 20:219.

20. Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, et al. Changing target temperature from 33 degrees C to 36 degrees C in the ICU management of out-of-hospital cardiac arrest: A before and after study. Resuscitation 2017; 113:39-43.

21. Topjian AA, French B, Sutton RM, Conlon T, Nadkarni VM, Moler FW, et al. Association of Post-Resuscitation Hypotension with Survival Outcomes following Pediatric Cardiac Arrest. Crit Care Med 2014; 42: 1518-23.

22. Topjian AA, Telford R, Holubkov R, Nadkarni VM, Berg RA, Dean JM, Moler FW. The Association of Early Post-Resuscitation Hypotension with Discharge Survival following Targeted Temperature Management for Pediatric Out of Hospital Cardiac Arrest. JAMA Pediatr. 2018; 172:143-153.

23. Jacobshagen C, Pelster T, Pax A, Horn W, Schmidt-Schweda S, Unsold BW, et al. Effects of mild hypothermia on hemodynamics in cardiac arrest survivors and isolated failing human myocardium. Clin Res Cardiol. 2010; 99:267-76. .

24. Zobel C, Adler C, Kranz A, Seck C, Pfister R, Hellmich M, et al. Mild therapeutic hypothermia in cardiogenic shock syndrome. Crit Care Med. 2012; 40:1715-23.

25. Dalrymple-Hay MJ, Deakin CD, Knight H, Edwards JC, Keeton B, Salmon AP, Monro JL. Induced hypothermia as salvage treatment for refractory cardiac failure following paediatric cardiac surgery. Eur J Cardiothorac Surg 1999; 15: 515–518.

26. Anderson KB, Poloyac SM, Kochanek PM, Empey PE. Effect of Hypothermia and Targeted Temperature Management on Drug Disposition and Response Following Cardiac Arrest: A

Comprehensive Review of Preclinical and Clinical Investigations. Ther Hypothermia Temp Manag. 2016; 6:169-179.

27. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017 318(1):57-67

28. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017; 318:1550-1560.

29. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, et al. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA. 2017; 25;318:341-350.

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Therapeutic Hypothermia after Paediatric Cardiac Arrest: Pooled Randomized Controlled Trials

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ABSTRACT

Background: Separate trials to evaluate therapeutic hypothermia after paediatric cardiac arrest for out-of-hospital and in-hospital settings reported no statistically significant differences in survival with favourable neurobehavioral outcome or safety compared to therapeutic normothermia. However, larger sample sizes might detect smaller clinical effects. Our aim was to pool data from identically conducted trials to approximately double the sample size of the individual trials yielding greater statistical power to compare outcomes.

Methods: Combine individual patient data from two clinical trials set in forty-one paediatric intensive care units in USA, Canada and UK. Children aged at least 48 hours up to 18 years old, who remained comatose after resuscitation, were randomized within 6 hours of return of circulation to hypothermia or normothermia (target 33.0°C or 36.8°C). The primary outcome, survival 12 months post-arrest with Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) score at least 70 (scored from 20-160, higher scores reflecting better function, population mean=100, SD=15), was evaluated among patients with pre-arrest scores ≥70.

Results: 624 patients were randomized. Among 517 with pre-arrest VABS-II scores ≥70, the primary outcome did not significantly differ between hypothermia and normothermia groups (28% [75/271] and 26% [63/246], respectively; relative risk, 1.08; 95% confidence interval [CI], 0.81 to 1.42; p=0.61). Among 602 evaluable patients, the change in VABS-II score from baseline to 12 months did not differ significantly between groups (p=0.20), nor did, proportion of cases with declines no more than 15 points or improvement from baseline [22% (hypothermia) and 21% (normothermia)]. One-year survival did not differ significantly between hypothermia and normothermia groups (44% [138/317] and 38% [113/ 297], respectively; relative risk, 1.15; 95% CI, 0.95 to 1.38; p=0.15). Incidences of blood-product use, infection, and serious cardiac arrhythmia adverse events, and 28-day mortality, did not differ between groups.

Conclusions: Analysis of combined data from two paediatric cardiac arrest targeted temperature management trials including both in-hospital and out-of-hospital cases revealed that hypothermia, as compared with normothermia, did not confer a significant benefit in survival with favourable functional outcome at one year.

Clinical Trial Registration: THAPCA-OH ClinicalTrials.gov number, NCT00878644. THAPCA-IH ClinicalTrials.gov number, NCT00880087

Key Words

Paediatric Cardiac Arrest;

Randomised Controlled Trials;

Targeted Temperature Management;

Therapeutic hypothermia;

Therapeutic Normothermia

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INTRODUCTION

Therapeutic hypothermia (hypothermia) as compared to therapeutic normothermia (normothermia) for treatment of comatose children resuscitated after out-of-hospital or in-hospital cardiac arrest did not confer a significant benefit in survival with favourable functional outcome in two independent, parallel trials which utilized identical study protocols(1,2). Current paediatric guidelines recommend either hypothermia or normothermia for target temperature management (TTM)(3). However, since effect sizes tested were in the range of 10 to 20 percent, uncertainty persists regarding optimal temperature management.

In the broad paediatric age range, there are multiple differences between cardiac arrests occurring in the out-of-hospital versus in-hospital setting including patient demographics, underlying pre-existing pathology, aetiology of cardiac arrest, response times and resuscitative skills of the initial responders, and survival rates (4). These differences informed a decision by the THAPCA trials investigators to enrol patients into two separate independent parallel clinical trials (ClinicalTrials.gov NCT00880087 and NCT00878644). However, a major challenge in paediatric cardiac arrest trials is recruitment of sufficiently large sample sizes to detect small clinically significant differences(5). As the underlying mechanism for potential benefit from hypothermia after a hypoxic-ischemic insult is similar in both paediatric populations, the THAPCA trial investigators proposed a secondary analysis of the comparative efficacy and safety of the two temperature interventions in the combined population of out-of-hospital and in-hospital cardiac arrest study cohorts. We report here the results of the pooled data analysis from these two trials which used identical protocols.

METHODOLOGY

Design

The two THAPCA trials were conducted in paediatric intensive care units (ICUs) at 41 enrolling children's hospitals in the United States, Canada, and United Kingdom. The rationale, study design, outcome selection process, protocol summary, 12-month pilot vanguard phase and individual trial outcomes were previously published (6-8). Funding for both trials was from the National Heart, Lung, and Blood Institute (NHLBI). The trial protocols differed only in the inclusion criteria definition of out-of-hospital and in-hospital cardiac arrest(1,2). The institutional review boards of all participating sites and the data-coordinating centre approved the protocol and informed consent documents. Site research coordinators collected all data, and statisticians at the data-coordinating centre (University of Utah) performed all analyses. Site training, data management and site monitoring were described in the Supplementary Appendix of each trial report(1,2). All site investigators vouched for their submitted data. The current pooled study was approved by the THAPCA executive committee prior to analysis of either of the THAPCA trials.

Patient Population

Children ≥48 hours and <18 years old who sustained cardiac arrest, required chest compressions for ≥ two minutes, and required mechanical ventilation after return of circulation, met inclusion criteria. Major exclusion criteria were scores of 5 or 6 on the Glasgow Coma Scale motor response subscale (scores range from 1 to 6, lower scores indicate worse function), inability to randomize within 6 hours of return of circulation, active and refractory severe bleeding, pre-existing illness with life expectancy less than 12 months, and lack of commitment to aggressive care. Full exclusion criteria lists were provided in the Supplementary Appendix of the two trial reports(1,2). Written informed consent from a parent or legal guardian was required.

Randomization and Intervention

Eligible patients were randomized to hypothermia or normothermia in a 1:1 ratio using permuted blocks stratified by clinical centre and age (younger than 2 years, 2 to 11 years, and 12 years or older).

Targeted temperature management (TTM) was actively maintained for 120 hours in both groups, as previously described(1,2). Participants assigned to hypothermia were pharmacologically paralyzed, sedated and cooled (or warmed if indicated) by surface cooling using a Blanketrol III cooling unit (Cincinnati SubZero, Cincinnati) with mattresses applied anteriorly and posteriorly, to achieve and maintain 33°C (range 32-34°C) core temperature for 48 hours. They were rewarmed over 16 hours or longer to target temperature 36.8°C (range 36-37.5°C) which was actively maintained throughout the remainder of the 120 hour intervention period. Patients randomized to normothermia received identical care except core temperature was actively maintained at 36.8°C (range 36-37.5°C) for 120 hours with the cooling unit. Dual central temperature monitoring (oesophageal, rectal, or bladder) and a servo-control mode were used. For patients supported with extracorporeal membrane oxygenation (ECMO) at the time of randomization or later, temperature was controlled with ECMO using a single central temperature monitor. All other aspects of care were determined by clinical teams.

Outcomes

The primary outcome was survival with favourable neurobehavioral outcome at 12 month follow-up, defined as an age-corrected standard score ≥70 on the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II)(9). The VABS-II has an age-corrected mean score of 100 (standard deviation, 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 pre-specified in the protocol, enrolled children with pre-arrest VABS-II scores below 70 (based on data from caregiver questionnaire completed at each site within 24 hours of randomization) were excluded only from the primary efficacy analysis. Patients with no baseline VABS-II available were considered eligible for the primary analysis if their baseline Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores were in normal or mild disability categories(10,11). Scores on these scales range from 1 to 6, with lower scores representing less disability; patients with scores of 1 or 2 on both scales were eligible for the primary analysis.

Secondary outcomes were change in neurobehavioral function, measured as the difference from pre-arrest baseline to 12 month measurement on the VABS-II (assigning deceased cases and those with

lowest possible VABS-II scores worst possible outcomes, regardless of baseline function) and survival at 12 months. Safety outcomes included the incidences of blood product use, infection, and serious arrhythmias through seven days, and 28-day mortality. The outcome assessment methodology was previously described(1,2).

Statistical Analysis

Individual patient data from both primary trial datasets were combined. Identical definitions, coding, reference units and data collection processes were used for each trial enabling combination without loss of data items. The efficacy analysis for the primary outcome was performed using a pre-specified modified intention-to-treat approach in both trials, excluding children with poor pre-arrest neurobehavioral function. Secondary efficacy outcomes were analysed among all children. Safety analyses were done by treatment received. The primary outcome and 12 month mortality were compared between assigned treatment groups using a Cochran-Mantel-Haenszel test stratified by categorized age and study. Change in VABS-II was analysed using van Elteren's modification of the Mann-Whitney test (12), stratifying by categorized age and study, treating death as the worst outcome and the lowest possible VABS-II score as the second-worst outcome. For this exploratory investigation, significance was declared at the 0.05 for all tests. The probability of survival to one year was evaluated by comparing survival curves between arms using a log-rank test stratified by age category. Univariate analysis of prognostic risk factors for survival independent of treatment group were analysed. Multivariable analysis for prognostic factors for neurobehavioral outcome have been presented previously for each trial(13,14). Analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Cohort

Both trials commenced on September 1, 2009 with THAPCA-OH patients enrolled through December 31, 2012 at 36 centres in USA and Canada (2 did not recruit) and THAPCA-IH patients enrolled until February 27, 2015 at 37 sites in the USA, Canada and UK (9 sites did not enrol). Forty-seven centres

in total participated in at least one of the THAPCA trials, with 6 centres not randomizing at least one case. The full CONSORT Diagram is described in Appendix Fig 1. A total of 4146 patients met inclusion criteria and were screened; 1221 had no trial exclusion criteria and were eligible for enrolment; and 624 were enrolled, 321 randomized to hypothermia and 303 to normothermia. Eight patients, who were assigned to hypothermia and three normothermia, did not receive an intervention and one normothermia patient received hypothermia therapy. Five hundred and seventeen patients had VABS-II scores ≥70 at baseline, prior to their cardiac arrest, and were eligible for the primary outcome assessment.

The baseline characteristics of the two temperature treatment groups were similar (Table 1). Overall median age was 1.5 years IQR [0.3, 7.1] with 63% male; 71% had one or more pre-existing medical condition most frequent being cardiac, lung or airway, and neurological conditions. Thirty percent (190/624) had a primary cardiac aetiology for their arrest, 9% (57/624) presented with a shockable rhythm (ventricular fibrillation or ventricular tachycardia); and the median estimated duration of chest compressions was 25 minutes IQR [12, 42.5]. Time from return of spontaneous circulation after cardiac arrest to target temperature following randomization for hypothermia group was Median 6.9 hours [Interquartile range (IQR) 5.6 to 8.8] and normothermia group 6.4 hours [IQR 5.3 to 8.4].

Outcomes

The proportion of survivors with the primary outcome VABS-II score ≥70 at 12 months was not significantly different between those treated with hypothermia (28%) compared to the normothermia intervention (26%); relative risk 1.08; 95% confidence interval [CI] 0.81 to 1.42; p=0.61. In patients included in the primary analysis who died or had a profound (VABS-II <45 or lowest) or moderate to severe disability (VABS-ll 45-69), there was also no significant difference in proportion of patients treated with either therapy (p=0.4) (Table 2). The secondary outcome of one year change in VABS-ll score from baseline score did not differ between groups (p=0.20); nor did the proportion in whom the VABS-ll score decreased by no more than 15 points (1 standard deviation) or improve differ (hypothermia 22% versus normothermia 21%) (Table 2).

Survival at 12 months for 614 patients, whose outcome status was known, did not differ between groups (hypothermia 44% vs. normothermia 38%; relative risk 1.15; 95% CI 0.95 to 1.38; p=0.15) (Table 2).

Survival duration was longer for patients receiving hypothermia; (Figure 1a, p=0.045). Sensitivity analysis revealed that this difference was due to the greater number of deaths occurring in the normothermia groupbetween days 0 to 3 (Figure 1b, p=0.91; Supplemental Figure 2, p=0.003). Specifically, a greater number of deaths occurred on day 0 in the normothermia group (19 versus 5) and the majority (12/19) were due to cardiovascular failure/futility (Table 3). By 12 months, the proportions of deaths by individual causes were similar for patients treated with hypothermia and normothermia. The majority of deaths were attributed to brain death (24.6% versus 24.9%), withdrawal of medical support in view of poor neurological prognosis (35.8 versus 31.4%), or cardiovascular failure/futility (21.2% versus 24.9%) (Table 3).

Prognostic factors for survival and for survival at 12 months with VABS-II ≥70 were analysed (Table 4). A cardiac aetiology of cardiac arrest, initial rhythm of ventricular fibrillation or ventricular tachycardia, shorter duration of cardiopulmonary resuscitation, fewer epinephrine doses, and cardiac arrest occurrence during a weekday (versus weekend) and during the day (versus night) were each associated with improved survival, independent of treatment arm. Children whose cardiac arrest occurred in-hospital compared to out-of-hospital were almost twice as likely to survive (OR 1.79 [1.29, 2.49]) and three times as likely to survive with VABS-II ≥70 (OR 3.09, 95% CI [2.04, 4.69]) (see Supplemental Table 1).

Safety

Safety outcome data were available for 314 in the hypothermia group and 298 in the normothermia group. The incidences of blood-product use, infection, and serious arrhythmias within seven days did not differ between these groups; nor did 28 day mortality significantly differ [hypothermia, 146/314(46%) versus normothermia, 159/298(53%), p=0.10; (see Supplemental Table 2).

DISCUSSION

In this analysis of pooled data from two identically conducted targeted temperature management randomized clinical trials(1,2), there was no significant improvement in survival with favourable neurobehavioral outcome, defined as a VABS-II score ≥70 for hypothermia (28%) versus normothermia (26%) groups. Additionally, the best change from baseline outcome, defined as a VABS-II score reduction by no more than 15 points (1 SD) at one year, was similar for hypothermia (22%) and normothermia (21%) groups. Mortality at one year was not statistically different by temperature intervention, although earlier

deaths in the first three days of intervention were observed with normothermia. Hypothermia and normothermia groups had comparable safety profiles for blood product utilization, infection, serious cardiac arrhythmia and 28-day mortality.

We were able to perform a pooled randomized control trial (RCT) analysis, as opposed to an individual patient data (IPD) meta-analysis, because the RCT protocols were identical with respect to all elements including data definitions, collection and handling procedures, and primary and secondary outcomes. In addition, the trials were initiated concurrently and predominantly at sites that participated in both THAPCA trials, minimizing temporal and site-specific effects between trials. The justification for conducting separate trials stemmed from analysis of a pre-trial planning cohort study that found differences in the aetiology of arrest, initial cardiac arrest rhythm, resuscitation skills of initial responders and survival outcomes between paediatric out-of-hospital and in-hospital cardiac arrest populations(4,15,16). In fact, the substantial difference in proportion of favourable outcomes between the IH and OH cohorts provides support for the decision to conduct separate trials in these two paediatric populations.

The current investigation was planned and approved by the trial executive committee prior to completion of either trial. By combining the two trial datasets in the current investigation, we were able to further explore the impact of hypothermia versus normothermia to ameliorate severe hypoxic-ischemic injury following paediatric cardiac arrest in a sample approximately twice the size of the original trials. However, in the pooled population as in the individual trials, there were no statistically significant differences for the primary or two secondary outcomes. The larger sample size gained by combining the two trials leads to more precise confidence intervals for treatment effect than in each individual trial, more conclusively ruling out even moderate benefits of hypothermia.

In this study, both treatment arms received 120 hours of active temperature control, to prevent fever (temperature >37.5°C), using surface temperature control devices, pharmacological sedation and neuromuscular blocking medication as required. Our findings are similar to a large adult trial of targeted temperature management (TTM) of 33°C versus 36°C for 36 hours(17), which found no statistically significant difference in outcomes. However, neither the adult nor the paediatric trials compared active TTM with no active temperature control. Recent reports of actual practice temperature management of

adult cardiac arrest describe a change in TTM from 33°C to 36°C(18-20). This practice has been accompanied by trends in less active cooling, greater exposure to fever, and worse clinical outcomes(20). The reports suggest an actual practice 'belief' that fever prevention can be achieved without protocol guided sedation, neuromuscular blockage and servo regulated cooling devices. A large ongoing adult trial of hypothermia (33°C) versus standard care avoiding early fever (>37.8°C) management after cardiac arrest may provide needed information to address this critical question (ClinicalTrials.gov Identifier: NCT02908308).

Although there was no overall difference in survival at 12 months, we found a difference in time to death between hypothermia and normothermia treatment groups (Figure 1a; p=0.045)**.** This difference was explained by more early deaths in the normothermia group during days 0 through 3 (Figure 1c; p=0.003). There are at least two reasons for this observation. First, for day 0, increased deaths due to cardiac failure in the normothermia group was observed, although this trend largely balanced out by day 3 (Table 3). This suggests hypothermia may have been protective or provided additional inotropic effects for the myocardium in the early post arrest period. Early hypotension in the first 6 to 12 hours post cardiac arrest is associated with worse outcome in children comatose after cardiac arrest(21,22). Hypothermia has been reported to reduce inotropic or vasopressor requirement and reduce/rebalance myocardial work to oxygen demand(23). Following adult cardiac arrest, hypothermia increases systemic vascular resistance leading to reduced vasopressor use and lower oxygen consumption(24). In children, hypothermia has been reported as a useful salvage therapy for severe low cardiac output syndrome post congenital heart disease surgery(25). The second identifiable factor associated with hypothermia was lower numbers of deaths through day 3 that were attributable to brain death or to poor neurological prognosis [hypothermia 10% (31/321) versus normothermia 19% (57/303); p=0.001](Table 3). This likely reflected delays in neurological prognostic and brain death assessments in hypothermic patients until at least 24 hours after normothermia was achieved; this common practice stemmed from consideration that sedative drugs administered concurrently with hypothermia could have prolonged clearance and thereby confound clinical assessments(26).

There are limitations with the current study. As described previously, caregivers and research staff in the ICU were aware of treatment assignments of patients, although the primary outcome one year VABS-

II interview assessments were performed by individuals who were unaware of treatment group assignment(1,2). We could not rule out the possibility of earlier death or determination by clinical teams of futility in the normothermia group, as discussed above. Although planned prior to the completion of the two THAPCA trials, this pooled analysis was performed after publication of the two primary trials when the results were known to the investigators. A major strength of this study was that pooling of individual patient data analysis was possible due to identical protocols and data definitions. The larger sample size provided greater statistical power to show potential differences in neurobehavioral, mortality and safety outcomes. The inclusion and exclusion criteria selected patients with identical high risk of neurological morbidity and mortality. The final inclusion of 15% (624/4146) of initially screened patients may limit the generalization of the study findings to all paediatric cardiac arrest patients. However, the current pooled study included a more heterogeneous and generalizable population than did either individual trial. Inclusion of patients stratified with less severe injury, excluding the most severe hypoxic ischemic arrests (e.g. sudden infant death syndrome), or selecting a more homogeneous population (e.g. drowning) might allow more focused assessment of TTM efficacy. Unanswered questions remain regarding optimal evaluation of TTM. Future trials should consider different durations and depth of cooling (27-29), earlier onset of TTM, more precise patient stratification based on acute brain injury biomarkers, and adjunctive neuroprotective agents.

In conclusion, this larger pooled cohort of patients who were comatose after paediatric cardiac arrest from in-hospital or out-of-hospital locations, therapeutic hypothermia did not confer a statistically significant benefit in survival with a good functional outcome compared to therapeutic normothermia. Both hypothermia and normothermia active temperature interventions had similar severe adverse event profiles.

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REFERENCES

1. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. N Engl J Med 2015; 372:1898-908.

2. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. N Engl J Med. 2017; 376:318-329.

3. de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, et al. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132(18 Suppl 2):S526-42.

4. Moler FW, Meert K, Donaldson AE, Nadkarni V, Brilli RJ, Dalton HJ, et al. for the Pediatric Emergency Care Applied Research Network. In-hospital versus out-of-hospital pediatric cardiac arrest: A multicenter cohort study. Critical Care Med 2009; 37:2259-2267.

5. Kanthimathinathan HK, Scholefield BR. Dilemmas in undertaking research in paediatric intensive care. Archives of disease in childhood 2014;99:1043-9.

6. Moler FW, Silverstein FS, Meert KL, Clark AE, Holubkov R, Browning B, et al. Rationale, Timeline, Study Design and Protocol Overview of the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials. Pediatr Critical Care Med 2013; 14:e304-15.

7. Pemberton VL, Browning B, Webster A, Dean JM, and Moler FW. Therapeutic Hypothermia after Pediatric Cardiac Arrest Trial: The Vanguard Phase Experience and Implications for other Trials. Pediatr Critical Care Med 2013; 14:19-26.

8. Holubkov R, Clark AE, Moler FW, Slomine BS, Christensen JR, Silverstein FS, et al. Efficacy outcome selection in the Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) Trials. Pediatr Crit Care Med 2015; 16, 1-10.

9. Sparrow S, Cicchetti D, Balla D: Vineland Adaptive Behavior Scales. 2nd Edition. Minneapolis, MN: Pearson Assessment, 2005.

10. Fiser DH. Assessing the outcome of pediatric intensive care. J Pediatr 1992; 121:68-74.

11. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, and Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow- up

12. van Elteren PH. On the combination of independent two sample tests of Wilcoxon. Bulletin of the Institute of International Statistics 1960; 37:351–361.

13. Meert K, Telford R, Holubkov R, Slomine BS, Christensen JR, Berger J, et al. Cardiac Arrest Characteristics and their Association with Survival and Neurobehavioral Outcome after Pediatric Out-of-Hospital Cardiac Arrest. Pediatr Crit Care Med. 2016; 17(12):e543-e550.

14. Meert K, Telford R, Holubkov R, et al. Paediatric In-Hospital Cardiac Arrest: Factors associated with Survival and Neurobehavioural Outcome One Year Later. Resuscitation. 2018; 124:96-105.

15. Meert KL, Donaldson A, Nadkarni V, Tieves KS, Schleien CL, Brilli RJ, et al. Multicenter Cohort Study of In-Hospital Pediatric Cardiac Arrest. Pediatr Crit Care Med 2009; 10:544-553.

16. Moler FW, Donaldson AE, Meert K, Brilli RJ, Nadkarni V, Shaffner DH, et al. for the Pediatric Emergency Care Applied Research Network (PECARN). Multicenter Cohort Study of Out-of-Hospital Pediatric Cardiac Arrest. Crit Care Med 2011; 39:141-9.

17. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369:2197-206.

18. Deye N, Vincent F, Michel P, Ehrmann S, da Silva D, Piagnerelli M, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. Ann Intensive Care 2016; 6:4.

19. Nolan JP, Ferrando P, Soar J, Benger J, Thomas M, Harrison DA, Perkins GD. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. Crit Care 2016; 20:219.

20. Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, et al. Changing target temperature from 33 degrees C to 36 degrees C in the ICU management of out-of-hospital cardiac arrest: A before and after study. Resuscitation 2017; 113:39-43.

21. Topjian AA, French B, Sutton RM, Conlon T, Nadkarni VM, Moler FW, et al. Association of Post-Resuscitation Hypotension with Survival Outcomes following Pediatric Cardiac Arrest. Crit Care Med 2014; 42: 1518-23.

22. Topjian AA, Telford R, Holubkov R, Nadkarni VM, Berg RA, Dean JM, Moler FW. The Association of Early Post-Resuscitation Hypotension with Discharge Survival following Targeted Temperature Management for Pediatric Out of Hospital Cardiac Arrest. JAMA Pediatr. 2018; 172:143-153.

23. Jacobshagen C, Pelster T, Pax A, Horn W, Schmidt-Schweda S, Unsold BW, et al. Effects of mild hypothermia on hemodynamics in cardiac arrest survivors and isolated failing human myocardium. Clin Res Cardiol. 2010; 99:267-76. .

24. Zobel C, Adler C, Kranz A, Seck C, Pfister R, Hellmich M, et al. Mild therapeutic hypothermia in cardiogenic shock syndrome. Crit Care Med. 2012; 40:1715-23.

25. Dalrymple-Hay MJ, Deakin CD, Knight H, Edwards JC, Keeton B, Salmon AP, Monro JL. Induced hypothermia as salvage treatment for refractory cardiac failure following paediatric cardiac surgery. Eur J Cardiothorac Surg 1999; 15: 515–518.

26. Anderson KB, Poloyac SM, Kochanek PM, Empey PE. Effect of Hypothermia and Targeted Temperature Management on Drug Disposition and Response Following Cardiac Arrest: A

Comprehensive Review of Preclinical and Clinical Investigations. Ther Hypothermia Temp Manag. 2016; 6:169-179.

27. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017 318(1):57-67

28. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017; 318:1550-1560.

29. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, et al. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA. 2017; 25;318:341-350.

Table 1 - Demographics by Treatment

	Treatment Assigned		
	Hypothermia (N = 321)	Normothermia (N = 303)	P-value
Age at Randomization (years)			0.072[1]
N	321	303	
Median [Q1 - Q3]	1.7 [0.4 - 7.6]	1.2 [0.3 - 6.5]	
Age Group at Randomization			0.509[2]
< 2 years	173 (53.9%)	177 (58.4%)	
2-11 years	96 (29.9%)	80 (26.4%)	
>= 12 years	52 (16.2%)	46 (15.2%)	
Male	199 (62.0%)	193 (63.7%)	0.660[2]
Pre-existing Conditions			
No pre-existing condition	94 (29.3%)	88 (29.0%)	0.947[2]
Lung or airway disease	87 (27.1%)	89 (29.4%)	0.529[2]
Neurologic condition	87 (27.1%)	67 (22.1%)	0.148[2]
Gastrointestinal disorder	69 (21.5%)	72 (23.8%)	0.499[2]
Prenatal condition	59 (18.4%)	64 (21.1%)	0.389[2]
Congenital heart disease	111 (34.6%)	112 (37.0%)	0.535[2]
Other pre-existing condition	46 (14.3%)	53 (17.5%)	0.280[2]
Primary aetiology of cardiac arrest			0.663[2]
Cardiac	99 (30.8%)	91 (30.0%)	
Respiratory	156 (48.6%)	157 (51.8%)	
Other/Unknown	66 (20.6%)	55 (18.2%)	
Initial rhythm noted by EMS or hospital			0.903[2]
Asystole	99 (30.8%)	97 (32.0%)	
Bradycardia	104 (32.4%)	104 (34.3%)	
Pulseless electrical activity (PEA)	58 (18.1%)	54 (17.8%)	
Ventricular fibrillation or tachycardia	31 (9.7%)	26 (8.6%)	

Table 1 - Demographics by Treatment

	Treatment Assigned		
	Hypothermia (N = 321)	Normothermia (N = 303)	P-value
Unknown	29 (9.0%)	22 (7.3%)	
Estimated duration of chest compressions			0.133[1]
N	312	300	
Median [Q1 - Q3]	24.5 [10.5 - 40.0]	25.5 [12.5 - 48.0]	
Time of ROSC			0.961[2]
Day	222 (69.2%)	209 (69.0%)	
Night	99 (30.8%)	94 (31.0%)	
Day of ROSC			0.698[2]
Weekday	248 (77.3%)	238 (78.5%)	
Weekend	73 (22.7%)	65 (21.5%)	
Total known adrenaline (epinephrine) doses[3]			0.337[1]
N	320	302	
Median [Q1 - Q3]	3.0 [2.0 - 6.0]	4.0 [2.0 - 7.0]	
ECMO[4]	87 (27.1%)	97 (32.0%)	0.179[2]

[1] P-value is based on the Wilcoxon rank-sum test.
[2] Chi-squared test of no association.
[3] Administered by EMS and at hospital.
[4] Started at or before treatment and not stopped before treatment initiation.

Table 2. Primary and Secondary Outcomes.*

	Treatment Assigned				
	Hypothermia	Normothermia	Risk Difference	Relative Risk	P Value
Primary Outcome					
Survival at 12 months with VABS ≥ 70	75/271 (28%)	63/246 (26%)	2.1 (-5.6, 9.7)	1.08 (0.81, 1.42)	0.61†
One year status (detailed)					0.40‡
Death	152/271 (56%)	155/246 (63%)			
Profound disability (VABS < 45 or lowest possible)§	18/271 (7%)	11/246 (4%)			
Moderate to severe disability (VABS 45-69)¶	26/271 (10%)	17/246 (7%)			
Good functional status (VABS ≥ 70)‖	75/271 (28%)	63/246 (26%)			
Secondary Outcomes					
Survival at 12 months	138/317 (44%)	113/297 (38%)	5.5 (-2.3, 13.2)	1.15 (0.95, 1.38)	0.15†
One year change from baseline					0.20**
Death	179/315 (57%)	184/287 (64%)			
Lowest possible VABS score	7/315 (2%)	1/287 (0%)			
VABS decreased > 30 points	31/315 (10%)	23/287 (8%)			
VABS decreased 16-30 points	28/315 (9%)	18/287 (6%)			
VABS decreased no more than 15 points or improved	70/315 (22%)	61/287 (21%)			

* The primary outcome was evaluated in patients with a baseline Vineland Adaptive Behaviour Scales, Second Edition (VABS-II), score of 70 or higher at 12 months (scores on the VABS-II range from 20 to 160, with higher scores indicating

better function). The secondary outcomes were evaluated in all patients with available data. Denominators reported are for patients whose outcomes were known. CI denotes confidence interval.

† The P value was calculated by means of the Cochran-Mantel-Haenszel test, with adjustment for age category and study.

‡ The P value was calculated by means of the Mann-Whitney test on the basis of the 1-yr continuous VABS-II score, stratified according to age category and study. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of -2000 and -1000, respectively (i.e., the worst possible scores).

§ Profound disability was defined as a VABS-II score of less than 45 or the lowest possible score.

¶ Moderate-to-severe disability was defined as a VABS-II score of 45 to 69.

‖ Good functional status was defined as a VABS-II score of 70 or higher.

** The P value was calculated by means of the Mann-Whitney test on the basis of the continuous change in VABS-II score, stratified according to age category and study. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of -2000 and -1000, respectively (i.e., the worst possible scores).

Table 3. Cause of Death by Study Day.

Hypothermia

	Study Day							
	0 (N = 5)	1 (N = 30)	2 (N = 17)	3 (N = 14)	4 (N = 21)	5 (N = 9)	> 5 (N = 83)	Overall (N = 179)
Cause of Death								
Cardiovascular failure/futility	4 (80.0%)	8 (26.7%)	7 (41.2%)	2 (14.3%)	1 (4.8%)	0 (0.0%)	16 (19.3%)	38 (21.2%)
Brain death declared	0 (0.0%)	3 (10.0%)	2 (11.8%)	4 (28.6%)	12 (57.1%)	6 (66.7%)	17 (20.5%)	44 (24.6%)
Withdrawal for poor neurologic prognosis	0 (0.0%)	11 (36.7%)	5 (29.4%)	6 (42.9%)	8 (38.1%)	3 (33.3%)	31 (37.3%)	64 (35.8%)
Respiratory failure/futility	0 (0.0%)	1 (3.3%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.6%)	5 (2.8%)
Withdrawal for other system failure	1 (20.0%)	3 (10.0%)	2 (11.8%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	6 (7.2%)	14 (7.8%)
Other/Unknown	0 (0.0%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (12.0%)	14 (7.8%)

Normothermia

	Study Day							
	0 (N = 19)	1 (N = 29)	2 (N = 22)	3 (N = 22)	4 (N = 18)	5 (N = 10)	> 5 (N = 65)	Overall (N = 185)
Cause of Death								
Cardiovascular failure/futility	12 (63.2%)	6 (20.7%)	2 (9.1%)	3 (13.6%)	1 (5.6%)	2 (20.0%)	20 (30.8%)	46 (24.9%)
Brain death declared	0 (0.0%)	11 (37.9%)	11 (50.0%)	8 (36.4%)	7 (38.9%)	5 (50.0%)	4 (6.2%)	46 (24.9%)
Withdrawal for poor neurologic prognosis	3 (15.8%)	9 (31.0%)	6 (27.3%)	9 (40.9%)	9 (50.0%)	2 (20.0%)	20 (30.8%)	58 (31.4%)
Respiratory failure/futility	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	8 (12.3%)	10 (5.4%)
Withdrawal for other system failure	2 (10.5%)	2 (6.9%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (9.2%)	12 (6.5%)
Other/Unknown	2 (10.5%)	0 (0.0%)	1 (4.5%)	1 (4.5%)	1 (5.6%)	1 (10.0%)	7 (10.8%)	13 (7.0%)

Figure Legends

Figure 1a. Probability of survival to one year following cardiac arrest, according to assigned treatment.

The two lines represent Kaplan-Meier survival rates from 0 to 365 days after cardiac arrest for patients in each study arm (p=0.045 for a log-rank test, stratified by age category and study, comparing survival distributions between treatment arms). Numbers above the x-axis represent numbers of patients at risk (alive and followed) in each study arm at each 30-day interval.

Figure 1b. Probability of survival past day 3 to one year following cardiac arrest, according to assigned treatment.

The two lines represent Kaplan-Meier survival rates from 4 to 365 days after cardiac arrest for patients in each study arm (p=0.912 for a log-rank test, stratified by age category and study, comparing survival distributions between treatment arms). Numbers above the x-axis represent numbers of patients at risk (alive and followed) in each study arm at each 30-day interval.

Figure 1a. Kaplan-Meier estimates of survival probability

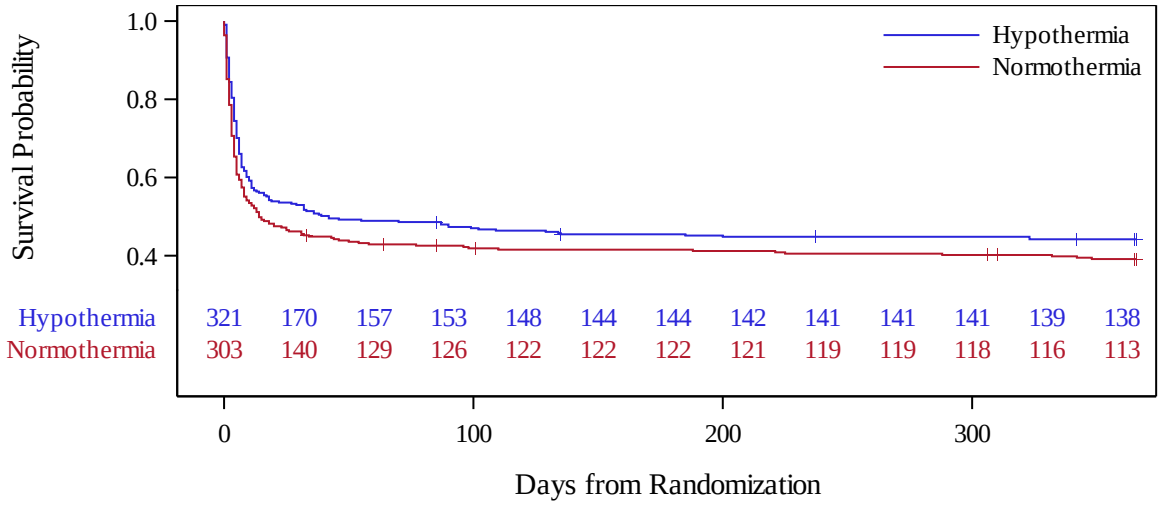
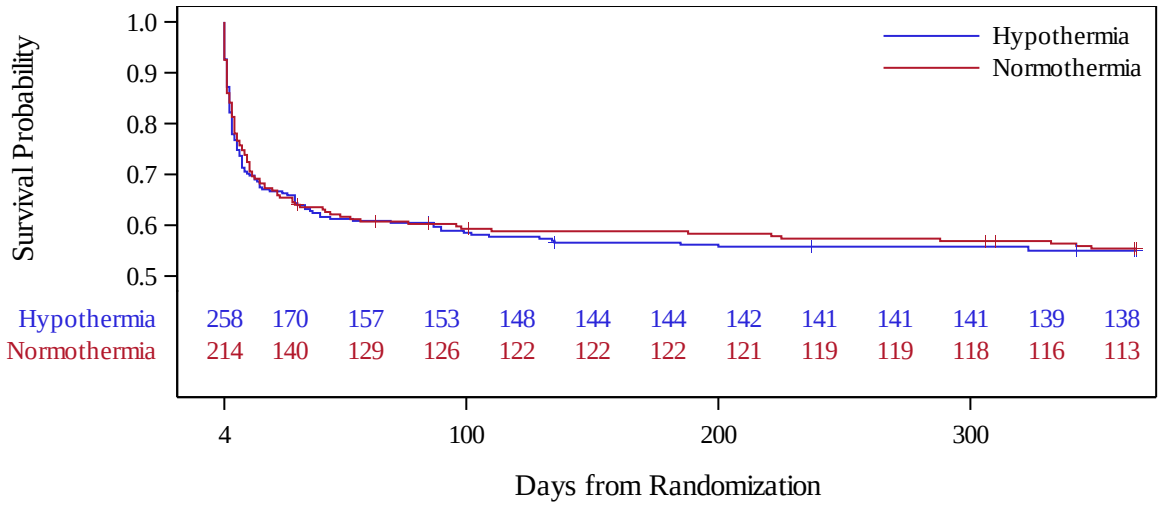


Figure 1b. Kaplan-Meier estimates of survival probability (Subjects surviving past day 3)



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