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24 vs. 72 Hours of Hypothermia for Pediatric Cardiac Arrest: A Pilot, Randomized Controlled Trial

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Abstract

Aim—Children surviving cardiac arrest (CA) lack proven neuroprotective therapies. The role of biomarkers in assessing response to interventions is unknown. We hypothesized that 72 versus 24 h of hypothermia (HT) would produce more favorable biomarker profiles after pediatric CA.

Methods—This single center pilot randomized trial tested HT ($33 \pm 1^\circ\text{C}$) for 24 vs. 72 h in 34 children with CA. Children comatose after return of circulation aged 1 week to 17 years and treated with HT by their physician were eligible. Serum was collected twice daily on days 1-4 and once on day 7. Mortality was assessed at 6 months.

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Results—Patient characteristics, baseline biomarker concentrations, and adverse events were similar between groups. Eight (47%) and 4 (24%) children died in the 24 h and 72 h groups, $p=0.3$. Serum neuron specific enolase (NSE) concentration was increased in the 24 vs. 72 h group at 84 h - 96 h (median [interquartile range] 47.7 [3.9, 79.9] vs. 1.4 [0.0, 11.1] ng/ml, $p=0.02$) and on day 7 (18.2 [3.2, 74.0] vs. 2.6 [0.0, 12.8] ng/ml, $p=0.047$). Serum S100b was increased in the 24 h vs. 72 h group at 12 h- 24 h, 36 h – 84 h, and on day 7, all $p<0.05$. HT duration was associated with S100b (but not NSE or MBP) concentration on day 7 in multivariate analyses.

Conclusion—Serum biomarkers show promise as theragnostic tools in pediatric CA. Our biomarker and safety data also suggest that 72 h duration after pediatric CA warrants additional exploration.

Keywords

Critical care; Neurologic disorders; Pediatric; Cardiac arrest; Biomarker; Outcome

INTRODUCTION

Children with cardiac arrest (CA) have mortality rates approaching 50% for in-hospital and 80-90% for out-of-hospital events, with many survivors having neurological disability and patients lacking neuroprotective therapies¹⁻⁸. Blood-based biomarkers including neuron specific enolase (NSE), S100b, and myelin basic protein (MBP), originating from neurons, astrocytes, and myelin, respectively, may be helpful to assist in selecting patients for therapies and as theragnostic and prognostic tools in patient care and research⁹⁻¹¹.

Clinical trials initially showed that hypothermia (HT) at 32-34°C improved outcomes in adults with out-of-hospital CA (12 and 24 h duration) and in neonates with birth asphyxia 72 hours (h) of HT is standard of care¹²⁻¹⁶. Since the initiation of this study, the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trials in children with CA detected no superiority of 48 h of HT versus controlled normothermia^{17,18} and a controlled temperature of 36°C are not superior to 33°C for targeted temperature management (TTM) in adults¹⁹.

Our unit practice at the time of study initiation (prior to participating in THAPCA) was in favor of the use of HT but was unprotocolized²⁰. The objective of this single center randomized pilot trial was to evaluate two HT durations for feasibility and safety. We selected durations with evidence of efficacy in other populations: adults (24 h) and neonates (72 h). We hypothesized that patients in the 72 h HT group would have more favorable brain injury blood biomarker levels compared to patients in the 24 h HT group.

METHODS

Study Period

This trial was conducted between November 2009 and December 2013. The University of Pittsburgh Institutional Review Board approved the RCT (NCT00797680) at the Children's Hospital of Pittsburgh.

Enrollment of Patients

We enrolled 34 children between the ages 1 week and 17 years who were admitted to the ICU with return of spontaneous circulation (ROSC) after in- or out-of-hospital CA. CA was defined as receipt of chest compressions for pulselessness by a healthcare worker. Subjects were included if they had an indwelling arterial or venous catheter for blood draws, had a Glasgow Coma Scale score ≥ 8 after ROSC, and had HT initiated by their ICU attending. Subjects were excluded if they had a do not resuscitate status, were pregnant, had any contraindication for MRI, had another simultaneous acute brain disease (including traumatic brain injury), were undergoing brain death evaluation, had a metabolic disease affecting the brain, or had active hemorrhage or a pre-existing coagulation defect. Children enrolled in this study who had a clinical brain MRI also had brain MR Spectroscopy performed; imaging results will be reported separately. Enrollment in this study began one year prior to THAPCA. Once THAPCA was approved at our center, we prioritized enrollment in THAPCA. Children that did not qualify for THAPCA were then evaluated for inclusion in this study.

Consent, Randomization, and Intervention

Informed consent was obtained from the subject's parent or guardian by the primary investigator or qualified co-author. Subjects were assigned a group through stratified block randomization, with CA location (in vs. out of hospital) as strata given differences in outcomes for pediatric CA, using computer assignment. Randomization schedule was generated by a statistician's software program and stored in sealed envelopes. Since HT was initiated for clinical reasons the intervention was already started prior to the consent process.

Temperature Control

All subjects had continuous temperature monitoring in two anatomical locations (esophageal, rectal, bladder catheter, and/or extracorporeal circuit probes). All patients were treated using a cooling blanket. Other measures of temperature control were applied as needed including cold saline infusion, cold packs, room temperature regulation, and tepid bath. HT was maintained at $33 \pm 1^\circ\text{C}$ for either 24 or 72 h based on assignment. Once the goal treatment duration was achieved, patients were rewarmed by 0.5°C every 4 h to normothermia (37°C)²¹.

Patient Care

We previously described post-resuscitation care in our PICU including prevention of secondary neurologic insults, treatment of organ dysfunction, and investigation of cause of CA if unknown^{22,23}. Subjects in both groups received similar care except for the study intervention.

Data Collection

We collected data collected from medical charts using the Utstein template for CA, including subject demographics, details about the CA and resuscitation, post-resuscitation care and treatment, and adverse events²⁴.

Serum Biomarkers

Three milliliters of blood were collected twice daily (days 1-4) and once on day 7 after ROSC. Samples were centrifuged, aliquoted, frozen at -70°C, and analyzed in batches. Serum NSE, S100b, and MBP were measured in duplicate using commercially available ELISAs (International Point of Care, Toronto, Ontario, Canada). NSE concentration was corrected for hemolysis²⁵. The sensitivity of the assays was 0.1 ng/mL for NSE and MBP and 0.01 ng/mL for S100b. The coefficient of variation for each assay was < 10%. An experienced technician blinded to subject treatment and outcomes performed all biomarker measurements. Clinical team members were unaware of the biomarker results. Samples were assessed in 12 hour blocks from ROSC due to time-dependent changes in biomarkers and one time at 7 days for all analyses. No sample time points were missed from living subjects but not all survived to day 7. Higher serum concentrations of the biomarkers studied here are associated with injury and potential for worse outcome{Berger, 2005 #4703}{Fink, 2014 #8299}.

Follow-up evaluations

The PI assigned the pre-arrest, hospital discharge, and 6 month Pediatric Cerebral Performance Category (PCPC) scores, and was blinded to biomarker results but not to clinical course. Six month outcomes were performed in surviving children either over the telephone (almost always) or during in-person interview with the parent or guardian during a scheduled outpatient visit.

Outcome Measures

The primary outcome was serum biomarker concentrations on day 7 (post-rewarming) by randomized group. Secondary outcomes included unfavorable outcome and mortality at 6 months post-CA. Unfavorable outcome was defined as PCPC score 4, 5, or 6 or increase >1. Adverse events were assessed through the PICU stay or 28 days, whichever was shortest.

Sample size

Our sample size was derived to detect significant differences between our two treatment groups and was driven by the variable serum NSE. We choose to have an equal number of subjects in each group. Based on Tiainen, et al, we assume that the range of standard deviation is 2.0-4.0 µg/ml{Tiainen, 2003 #4254}. We assumed that the concentration of serum NSE in 72 h HT group would have the same standard deviation as that in 24 h HT group. In the following sample size calculations, the type I error rate is set as .05 and power=80%.

Twenty subjects were targeted for recruitment for each treatment group. Power calculations were based on 18 subjects per treatment group after accounting for an anticipated 10-15% attrition rate. Type I error rate is .05. The study was designed to have 80% power to detect an effect size of 0.85 between groups for NSE concentration.

Statistical Analyses

All analyses were conducted using SAS® 9.2 (Copyright © [2002-2008] SAS Institute Inc., Cary, NC, USA). Frequencies and percentages were determined for categorical variables. Biomarker data are presented as median (interquartile range [IQR]) since data were skewed. Other continuous variables are presented as mean and standard deviation (SD). All p-values were 2-sided, and a $p < 0.05$ was considered statistically significant. NSE, S100b, and MBP levels were graphed by 12 h interval post-ROSC and randomized group. Median (95th confidence interval [CI]) serum biomarker concentrations were represented graphically by randomized group. Samples closest to but not after 12 h, 24 h, etc. were chosen to represent that time point. If more than one serum biomarker fell within a 12 h interval the maximum biomarker value was chosen to represent that time point. Group differences in daily biomarker values and other continuous data were compared using the Wilcoxon Rank Sum and Kruskal-Wallis tests. Differences in categorical data were assessed using chi-square analysis with Fisher's Exact test when appropriate.

Multivariate linear regression models were used to evaluate how biomarker concentrations, treatment group, and other clinical variables affected biomarker concentration on day 7. We first assessed univariate cohort differences in the risk factors listed in table 1 using either X^2 or t tests. Characteristics that were found to have $p < 0.10$ were selected for inclusion in multivariate analysis²⁶. Multivariate linear regression was then conducted to examine differences between cohorts in the level of biomarker at day 7. Clinical and demographic variables having a p-value ≤ 0.4 in bivariate analyses were tested in multivariate linear regression models. These models were then reduced to the most parsimonious model by including factors with a p value of 0.2 or less in a stepwise manner. All participants were included in outcome analysis using intention-to-treat approach.

RESULTS

Patients

We screened 293 children for eligibility of which 75 met inclusion criteria. Thirty-four subjects were enrolled with 17 in each group (Figure 1). Of those not enrolled, 18 were already enrolled in another interventional trial, and 14 families refused consent. The most common reasons for exclusion were for lack of comatose status ($n=94$), lack of ROSC ($n=35$), and clinically significant bleeding ($n=32$). All children received their assigned intervention, but two children in the 72 h group did not receive the entire treatment due to concern for futility - one child was rewarmed after 43 h of HT and subsequently progressed to brain death while the other child had supportive care withdrawn without rewarming during the treatment period. No families withdrew their child from the study, and no children were lost to follow-up.

Baseline patient characteristics and CA details were not different between the two treatment groups (Table 1). Eighty-eight per cent of arrests were due to asphyxia, 82% occurred out-of-hospital, and the median (interquartile range [IQR]) duration of cardiopulmonary resuscitation was 20 (11.5, 30.0) minutes. All children had at least 2 minutes of cardiopulmonary resuscitation. One child with congenital heart disease had an in-hospital

CA and was resuscitated using extracorporeal cardiopulmonary resuscitation. Baseline (0-12 h post-ROSC) biomarker concentrations were not different between the groups. Twelve (35%) children died overall, 8 (47%) in the 24 h group and 4 (24%) in the 72 h group, $p=0.3$. There were 11 (65%) and 10 (59%) children with unfavorable outcomes in the 24 and 72 h groups, respectively.

Intervention—Figure 2 shows the temperature curves by treatment group. Median time to target temperature overall was 0 (0-2) h [mean $\pm$ standard deviation 2.4 ± 4.3 h]. Time to target temperature for the 24 h group was 0 (0-2) h [1.8 ± 3.6] vs. for the 72 h group 0 (0-6) h [3.0 ± 5.0], $p=0.6$. Median duration of HT within the target temperature range was 30 (27-33) [30.8 ± 5.0] h and 78 (75-79) [76.6 ± 24.1] h for the 24 and 72 h groups, respectively.

Serum Biomarker Concentrations and Outcome—Figures 3a-c present serum biomarker concentrations (median [95% confidence interval (CI)]) by group. Overall, all serum biomarker concentrations after 0-12 h were numerically higher in the 24 vs. 72 h group except MBP day 7. Serum NSE concentration was increased in the 24 h vs. 72 h group at 84 h - 96 h (47.7 (3.9, 79.9) vs. 1.4 (0.0, 11.1) ng/ml, $p=0.02$) and on day 7 (18.2 (3.2, 74.0) vs. 2.6 (0.0, 12.8) ng/ml, $p=0.047$). Serum S100b was increased in the 24 h vs. 72 h group at 12 h - 24 h, 36 h - 84 h, and on day 7, all $p<0.05$. Serum MBP was increased in the 24 h vs. 72 h group at 36 h - 48 h (0.302 (0.115, 0.612) vs. 0.102 (0.074, 0.169), $p=0.049$).

Multivariable analysis for day 7 biomarker concentrations—Treatment group was not associated with NSE or MBP concentrations on day 7 in multivariable analysis after controlling for age, CPR duration, and number of epinephrine doses (Table 2). Randomization to 24 h hypothermia was associated with higher S100b concentration on day 7 (parameter estimate -0.01, 95% confidence interval -0.0287-0.0005, $p = 0.04$).

Adverse events—There were no differences in the frequency of infection (12 vs. 24%), seizure (35% each), bleeding (6% each), or re-arrest (18 vs. 0%) between 24 and 72 h groups over the ICU course (Table 3).

DISCUSSION

This exploratory trial found that 72 h of HT therapy was associated with lower concentrations of brain injury biomarkers at multiple time points within the first week following pediatric CA versus 24 h. In addition, group differences remained significantly associated with S100b concentration on day 7 post-arrest in multivariable analysis. Finally, we could detect no difference in mortality and unfavorable outcome at 6 months and no difference in frequency of adverse events between groups.

Experimental models published before and after the completion of this study suggest that longer duration of HT may be more effective as a neuroprotective strategy than shorter duration²⁷⁻³⁰. Previous studies assessing HT for pediatric CA due to drowning did not protocolize duration of HT and were ultimately ineffective³¹. Our hospital's early experience using HT noted variable HT duration and target temperature application, lacking

tools to assess for best candidates and optimal therapy parameters and therapeutic monitoring that could best improve outcomes²⁰. Ultimately we chose to compare patients after 24 and 72 h HT, reflecting positive trials at the time in other populations with global hypoxic-ischemic injury¹²⁻¹⁵. Therefore, unlike most RCTs testing HT as a neuroprotectant, there was no normothermia group in our trial. During the course of our study, one small adult CA trial found no difference in outcome comparing 24 vs. 72 h HT while in neonates with birth asphyxia, 72 h at 33°C was confirmed as best clinical practice^{32,33}.

A growing body of literature shows robust association of serum NSE and S100b with outcomes after hypoxic-ischemic injury^{22,34-37}. Our primary outcome was the association between randomized treatment group and clinical variables with biomarker levels on day 7, reflecting concentrations in the post-rewarming period.

Although biomarker concentrations were similar at baseline for treatment groups, serum NSE and S100b concentrations were higher, and therefore more indicative of damage, in the 24 h group at many time points in univariate analysis. Tempering enthusiasm, however, S100b was increased in the 24 h group at the 12-24 hour interval, before any difference could be attributed to treatment intervention. Despite small sample size, randomized treatment group remained significant for S100b when adjusting for covariates, highlighting it as a serious candidate for validation as a clinical and research tool. In an RCT cohort of neonates with birth asphyxia, serum S100b was decreased more in infants in the HT vs. normothermia group at 48 h, paralleling their finding of better patient outcomes in the HT group³⁵. An early trial of HT vs. uncontrolled normothermia in adults with out-of-hospital CA found that serum NSE but not S100b concentrations were decreased in the HT group, which also had better outcomes than the control group¹¹. More recently, a large RCT of controlled HT and normothermia in adults found no difference in NSE levels between randomized groups, reflecting the lack of differences in outcome between groups³⁷. Whether serum NSE or S100b could be used as a theragnostic marker in pediatric CA interventional trials remains unknown, but consideration for biomarker assessment should be considered in future study design. For example, a threshold of biomarker concentrations may prove useful in determining eligibility for neuroprotective therapy trials or to optimize the dose and/or duration of neuroprotective therapy being tested or provided clinically. Additionally, combining biomarkers with clinical or other variables in a validated panel could noticeably strengthen associations and thus confidence as a clinical tool^{38,39}.

Similar to other RCTs in HT, there were no differences in serious adverse events between groups, but 72 h of HT has not been tested in large trials in pediatric CA^{17,18}.

Study limitations

There were several limitations to the design of this study. The small sample size precluded inclusion of all variables known to be associated with outcome in a multivariable analysis in this heterogeneous population. PCPC was assigned in a non-blinded fashion by the study PI (a pediatric intensivist) and obtained by interviewing the parent or guardian over the phone or sometimes in person. PCPC is a gross measure of function and may not accurately depict outcome in infants and young children⁴¹. In addition, HT cannot be blinded to the bedside caregivers. Patients in this pilot study may have differed from those enrolled in the

multicenter THAPCA trials and thus results are not generalizable. First, we did not separate results by CA location, and most children had out-of-hospital CA in this study. Median time to target temperature was not longer than in the THAPCA study, but time to randomization was 6 post-ROSC and up to 24 h in this study.

In summary, we need validated biomarkers that are related to clinical outcome, ideally with rapid results that would allow titration of clinical care. Biomarker choice, timing, and mechanism of injury affect biomarker trajectory, and testing requires thoughtful study design⁹. Future clinical trials can consider monitoring of biomarker response to therapeutic intervention as a supplement to other clinical outcomes. Thus far few trials have included longitudinal serum or imaging (i.e., MRI, transcranial doppler) biomarkers. These data may reveal subgroups eligible for personalized therapeutics: it is possible that some patients may benefit from different treatment regimens, and serial measurements may optimize benefit and minimize harm⁴⁰.

Our study also suggests that additional exploration of 72 h of HT is warranted in pediatric CA given that 1) a 72 h duration is standard of care in the treatment of birth asphyxia in term newborns, 2) CA in the PICU often occurs in infants, 3) our biomarker data may be supportive of using a 72 over a 24 h exposure, and 4) there were no differences in adverse effects.

CONCLUSION

Serum brain biomarkers show promise as theragnostic tools and need to be validated for clinical use in pediatric CA.

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This project is registered with clinicaltrials.gov (NCT00797680) as “Duration of Hypothermia for Neuroprotection after Pediatric Cardiac Arrest: A Randomized, Controlled Trial”

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Abbreviations

HT	Hypothermia
PICU	Pediatric intensive care unit
RCT	Randomized controlled trial
PCPC	Pediatric Cerebral Performance Category score

Figure 1.
CONSORT diagram for enrollment and outcomes.

Figure 2.

Patient hourly temperature curves by randomized group. Graph begins once patient has reached the target temperature (32-34°C). Data are presented as mean $\pm$ standard deviation.

Figure 3.

a-c. Serum NSE, S100b, and MBP biomarker concentrations by 12 hour intervals post-ROSC and randomized group.

* $p < 0.05$, randomized group difference, P-values for continuous variables are based on Wilcoxon rank tests.

Data presented as median (95% confidence interval).

Table 1

Patient Characteristics and Cardiac Arrest Details Overall and by Randomization Group.

	Overall N=34	24 h HT N=17	72 h HT N=17	95% Confidence Interval
Age, years	1.5 (0.3, 9.8)	0.6 (0.3, 3.0)	5.7 (0.3, 12.7)	
	4.9 ± 6.1	3.1 ± 5.4	6.6 ± 6.4	
Female sex	20 (59%)	8 (47%)	12 (71%)	
Race				
Black	10 (29%)	5 (29%)	5 (29%)	
White	23 (68%)	11 (65%)	12 (71%)	
Mixed/other race	1 (3%)	1 (6%)	0 (0%)	
Primary Etiology				0.03-3.13
Cardiac	4 (12%)	1 (6%)	3 (18%)	
Asphyxia	30 (88%)	16 (94%)	14 (82%)	
Location				0.17-5.83
In-hospital	6 (18%)	3 (18%)	3 (18%)	
Out-of-hospital	28 (82%)	14 (82%)	14 (82%)	
CPR to ROSC, min	20.0 (11.5, 30.0)	17.0 (10.0, 27.5)	25.5 (17.5, 30.0)	-18.00-0.00
	22.6 ± 14.5	18.1 ± 11.1	27.1 ± 16.4	
Epinephrine dose(s)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	3.0 (1.0, 3.0)	-1.00-2.00
	3.2 ± 2.7	3.8 ± 3.3	2.6 ± 1.9	
Defibrillated	4 (12%)	1 (6%)	3 (18%)	0.84-1.06
First monitored rhythm				1.000
Asystole	12 (35%)	6 (35%)	6 (35%)	
Pulseless electrical activity	18 (53%)	9 (53%)	9 (53%)	
Ventricular tachycardia or fibrillation	1 (3%)	0 (0%)	1 (6%)	
Sinus or other	3 (9%)	2 (12%)	1 (6%)	
Witnessed event	12 (35%)	5 (29%)	7 (41%)	0.41-6.96
Bystander resuscitation	27 (79%)	13 (76%)	14 (82%)	0.27-7.68
Hospital length of stay	19.0 (7.0, 30.0)	18.0 (4.0, 30.0)	22.0 (9.0, 26.0)	-16.00-8.00
	20.2 ± 15.6	17.9 ± 14.6	22.5 ± 16.8	
ICU length of stay	11.5 (6.0, 25.0)	9.0 (4.0, 23.0)	12.0 (8.0, 25.0)	-10.00-4.00

	Overall N=34	24 h HT N=17	72 h HT N=17	95% Confidence Interval
Disposition at hospital discharge	16.1 ± 13.9	14.2 ± 13.2	18.0 ± 14.7	
Home	11 (32%)	5 (29%)	6 (35%)	0.393
Inpatient rehabilitation	11 (32%)	4 (24%)	7 (41%)	
Died	12 (35%)	8 (47%)	4 (24%)	
Chronic disease	12 (35%)	5 (29%)	7 (41%)	0.41-6.96
Biomarker concentration 0-12 h (baseline)	N=30	N=14	N=16	
Neuron specific enolase	16.1 (9.6, 23.9)	14.0 (11.7, 23.9)	18.1 (7.1, 24.2)	-8.44-9.72
S100b	0.025 (0.012, 0.073)	0.029 (0.020, 0.111)	0.020 (0.009, 0.057)	-0.01-0.05
Myelin basic protein	0.157 (0.088, 0.238)	0.135 (0.088, 0.202)	0.168 (0.089, 0.390)	-0.17-0.06
Mortality at 6 months	12 (35%)	8 (47%)	4 (24%)	0.08-1.51
Unfavorable outcome at 6 months	21 (62%)	11 (65%)	10 (59%)	0.19-3.12

HT, hypothermia; ICU, intensive care unit

Note: Values expressed as n (%), mean ± standard deviation and/or median (25th, 75th percentiles)

Table 2

Multivariable linear regression analyses for the outcome of biomarker concentration on day 7.

	Parameter estimate	P value	95% CI
NSE			
24hr vs 72hr HT	-20.3521	0.162	-49.5210-8.8168
S100b			
24hr vs 72hr HT	-0.0146	0.043	-0.0287—0.0005
Age	-0.0008	0.145	-0.0020-0.0003
MBP			
24hr vs 72hr HT	-0.9761	0.299	-2.8758-0.9235

CI, confidence interval; NSE, neuron specific enolase; MBP, myelin basic protein

Variables initially included in backwards stepwise linear regression: randomized group, age, CPR to ROSC, and number of epinephrine doses

Table 3

Adverse events and protocol violations by randomized group.

	All (n=34)	24 h Hypothermia (n=17)	72 h Hypothermia (n=17)	P-value	95% Confidence Interval
Infection	6 (18%)	2 (12%)	4 (24%)	0.656	0.36-14.72
Seizures	12 (35%)	6 (35%)	6 (35%)	1.000	0.24-4.08
Bleeding	2 (6%)	1 (6%)	1 (6%)	1.000	0.06-17.41
Re-arrest	3 (9%)	3 (18%)	0 (0%)	0.227	0.66-1.03
Protocol violation	3 (9%)	0 (0%)	3 (18%)	0.227	0.97-1.51

Note: Values expressed as n (%)