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Clinical paper

Post-arrest therapeutic hypothermia in pediatric patients with congenital heart disease☆

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ABSTRACT

Background: While therapeutic hypothermia (TH) is an effective neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy, TH has not been demonstrated to improve outcome in other pediatric populations. Patients with acquired or congenital heart disease (CHD) are at high risk of both cardiac arrest and neurodevelopmental impairments, and therapies are needed to improve neurologic outcome. The primary goal of our study was to compare safety/efficacy outcomes in post-arrest CHD patients treated with TH versus controls not treated with TH.

Methods: Patients with CHD treated during the first 18 months after initiation of a post-arrest TH protocol (temperature goal: 33.5 °C) were compared to historical and contemporary post-arrest controls not treated with TH. Post-arrest data, including temperature, safety measures (e.g. arrhythmia, bleeding), neurodiagnostic data (EEG, neuroimaging), and survival were compared.

Results: Thirty arrest episodes treated with TH and 51 control arrest episodes were included. The groups did not differ in age, duration of arrest, post-arrest lactate, or use of ECMO-CPR. The TH group's post-arrest temperature was significantly lower than control's (33.6 ± 0.2 °C vs 34.7 ± 0.5 °C, $p < 0.001$). There was no difference between the groups in safety/efficacy measures, including arrhythmia, infections, chest-tube output, or neuroimaging abnormalities, nor in hospital survival (TH 61.5% vs control 59.1%, p = NS). Significantly more controls had seizures than TH patients (26.1% vs. 4.0%, p = 0.04). Almost all seizures were subclinical and occurred more than 24 h post-arrest.

Conclusion: Our data show that pediatric CHD patients who suffer cardiac arrest can be treated effectively and safely with TH, which may decrease the incidence of seizures.

Introduction

Therapeutic hypothermia (TH) has been studied as a neuroprotective therapy to minimize brain injury and improve neurologic outcome after hypoxic-ischemic encephalopathy (HIE) in several patient groups. The use of TH is well established for neonatal HIE, where it has been shown to improve both survival and neurodevelopmental outcome [1–5]. In other patient populations, TH has been utilized safely but without evidence of improved outcome [6–9].

Given the risk of hemodynamic instability and cardiac arrest in patients with acquired or congenital heart disease (CHD), neuroprotective therapies such as TH are needed to improve neurologic outcome. However, TH in CHD patients may involve greater risk, given that adverse events such as arrhythmia and bleeding may occur more frequently in CHD patients, particularly in the post-operative period.

The primary goal of our study was to compare safety and efficacy outcomes in patients with CHD treated under a TH protocol versus a group of historical and contemporary controls not treated with TH.

Methods

A clinical TH protocol was established in August 2013 for CHD

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patients who sustained a cardiac arrest within the cardiovascular program at our institution. Patients were considered for inclusion in the TH protocol if they had CHD and: 1. underwent cardiopulmonary resuscitation (CPR) for greater than 5 min, or 2. suffered cardiac arrest that was treated with extracorporeal membrane oxygenation cardiopulmonary resuscitation (ECMO-CPR). Inclusion in the TH protocol was at the discretion of the clinical team.

Patients

After obtaining approval for this retrospective study from the institutional review board, the Cardiovascular Program cardiac arrest database was searched to identify patients for this study. Patients were included if they were treated under the TH protocol in the first 18 months of its initiation (8/2013-1/2015, TH patients). Patients were considered as treated under the TH protocol if TH orders were placed in the medical record and/or the TH protocol was included in the daily notes. A comparison control group consisted of 2 sets of patients: 1. historical control patients who met criteria for TH (CPR > 5 min or ECMO-CPR) in the 18 months prior to initiation of the TH protocol (2/2012–7/2013), and 2. contemporary control patients who met criteria for the TH protocol in the first 18 months of its initiation (8/2013–1/2015) but were not treated under the TH protocol, based on the management decisions of the clinical team.

Therapeutic hypothermia protocol

Under the TH protocol, patient temperature was targeted to be 33.5 °C for either 72 h (< 1 year of age) or 48 h (≥1 year of age). Patients < 1 year of age were cooled for 72 h based on published neonatal trials, while patients ≥1 year of age were cooled 48 h based on the THAPCA trial.[3,4,8] Cooling was managed via the ECMO circuit or via cooling blanket for those not on ECMO. An esophageal temperature probe was placed for temperature monitoring. Patients were excluded from the protocol for known significant intracranial hemorrhage (large epidural, subdural, or parenchymal hemorrhage, or Grade III or IV intraventricular hemorrhage), pregnancy, or postmenstrual age < 36 weeks. Sedation and paralytic medications were not specified in the TH protocol, but were administered at the discretion of the clinical team. Monitoring during cooling included a minimum of 24 h of continuous video-electroencephalogram monitoring (cvEEG) and head ultrasound (HUS, every other day if fontanel open), and/or other brain imaging as clinically indicated. Other clinical and safety monitoring included daily electrolytes/hematologic profile, continuous telemetry, and measurement of chest tube losses (if applicable) and urine output.

Per protocol, patients were rewarmed at a rate of 0.5 °C every 2 h to a goal temperature of 36.5 °C, although goal temperature was set by the medical care team.

Clinical data

For TH patients, temperature and monitoring data were collected from time of arrest and through the rewarming period. For control patients, data were collected over a "therapeutic window" time period which paralleled the data collection time period for TH patients. The "therapeutic window" consisted of either 72 h (< 1 year of age) or 48 h (≥1 year of age) to represent the TH time period post-arrest, plus 12 h to represent rewarming. Thus, control patients had temperature and monitoring data collected for 84 h post-arrest if < 1 year of age and 60 h if ≥1 year of age.

Retrospective chart reviews were completed to collect demographic, cardiac, neurologic and other clinical data at the time of cardiac arrest and through the cooling and rewarming period or "therapeutic window" in controls. Data collected included location/duration of arrest, use of ECMO-CPR, and initial lactate measured after arrest. During cooling/rewarming in TH patients and the "therapeutic window" in control patients, temperatures, urine/chest tube output, arrhythmias, cultures (blood, sputum, urine, wound), and labs were recorded. Arrhythmias during the post-arrest period were examined to determine whether they occurred prior to arrest or had new onset post-arrest, and whether they required intervention (e.g. antiarrhythmic medications, direct current cardioversion, temporary pacing).

Any temperature > 38 °C was considered a fever, and any temperature < 32 °C was considered severe hypothermia. All head imaging performed was reviewed by a single pediatric neuroradiologist (AD). All cvEEGs were performed as part of the TH protocol or for other clinical indications, and were interpreted daily for clinical management. For this study, all cvEEGs were analyzed again by a single pediatric neurophysiologist (AJS) for presence of seizures, background features and state changes, per American Clinical Neurophysiology Society terminology [10]. The time to first seizure post-arrest was determined by the first clinical or subclinical seizure.

Table 1
Demographic and Medical Characteristics.

	Therapeutic Hypothermia	Control	p-value
Demographics			
Number of patients	26	49	
Male (% of patients)	12 (46.2%)	33 (67.3%)	0.08
Number of arrests	30	51	
Age at arrest (mo)	6.0 (0.9, 27.4)	2.5 (0.5, 13.2)	NS
Neonates (< 28 days at arrest)	7 (23%)	17 (33%)	NS
Gestational age at birth[a] (w)	39.0 (37.1, 39.4, n = 7)	38.4 (36.1, 39.3, n = 17)	NS
Single Ventricle Circulation	4 (13.3%)	21 (41.2%)	0.01
Pre-operative/Unpalliated	0	1 (4.8%)	NS
Stage 1	1 (25%)	10 (47.6%)	
Systemic to pulmonary Shunt	1 (25%)	6 (28.6%)	
Bidirectional Glenn	0	0	
Fontan	1 (25%)	3 (14%)	
Other	1 (25%)	1 (5%)	
Two Ventricle Circulation	26 (86.7%)	30 (58.8%)	0.01
Tetralogy of Fallot	4 (15%)	5 (17%)	NS
Heart transplant	4 (15%)	0	
Cardiomyopathy	3 (12%)	2 (7%)	
Complex heterotaxy	2 (8%)	7 (23%)	
Aortic arch obstruction	1 (4%)	5 (17%)	
Other[b]	12 (46%)	11 (37%)	
Arrest Details			
Arrest duration (min)	22.0 (14.0, 40.0)	21.0 (13.0, 33.0)	NS
Post-arrest pH	7.18 (7.06, 7.30) (n = 30)	7.23 (7.09, 7.35) (n = 51)	NS
Post-arrest lactate	11.7 (7.1, 17.0) (n = 28)	11.6 (9.2, 15.0) (n = 49)	NS
Post-operative arrest[c]	14 (46.7%)	33 (64.7%)	NS
ECMO-CPR	18 (60.0%)	37 (72.5%)	NS
Location of Arrest			
Cardiac ICU	22 (73.3%)	43 (84.3%)	NS
Cardiac floor	2 (6.7%)	1 (2.0%)	
Catheterization lab	3 (10.0%)	2 (3.9%)	
Cardiac OR	0	3 (5.9%)	
General OR	1 (3.3%)	2 (3.9%)	
Other	2 (6.7%)	0	

Number (%) or Median (IQR), % of arrests unless otherwise noted.
ECMO, Extracorporeal Membrane Oxygenation.
[a] Data only for neonates.
[b] No diagnosis with more than 2 patients.
[c] < 30 d from surgery.

Statistical analysis

Continuous measures are presented as medians and interquartile measures (P25, P75) or mean and standard deviation, as appropriate. The *t*-test or the non-parametric Wilcoxon rank sum test was used to