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102.03.11

Resuscitation 84 (2013) 189–193

Contents lists available at SciVerse ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

The effect of hypothermia "dose" on vasopressor requirements and outcome after cardiac arrest☆

Nicholas Huynh[a], John Kloke[b], Chen Gu[c], Clifton W. Callaway[d], Francis X. Guyette[d], Kory Gebhardt[e], Rene Alvarez[f], Samuel A. Tisherman[g], Jon C. Rittenberger[d,*]

[a] University of Southern California, Department of Internal Medicine, United States
[b] University of Wisconsin, Department of Internal Medicine, Division of General Internal Medicine, United States
[c] University of Pittsburgh, Department of Internal Medicine, Division of General Internal Medicine, United States
[d] University of Pittsburgh, Department of Emergency Medicine, United States
[e] University of Pittsburgh School of Medicine, United States
[f] Temple University, Department of Medicine, Section of Cardiology, United States
[g] University of Pittsburgh, Department of Critical Care Medicine and Surgery, United States

Introduction

- The Effect of therapeutic hypothermia(TH) on hemodynamic after cardiac arrest is unclear.
- The interaction between TH and hemodynamic instability is complex.
- whether patients receiving TH required more vasopressor or inotropic agents than normothermic patients
- whether dose of TH was related to survival and neurologic outcome among subjects treated with hypothermia

Method

- prospective quality improvement database
- adults (≥18 years) after cardiac arrest and return of pulses between 1/1/2005 and 3/15/2010.
- The goal temperature was 33 ◦C (32-34 also range)
- Fluid infusion and use of vasopressors and inotropes were recommended to achieve a urine output of ≥0.5 mL/kg/h and mean arterial pressure ≥ 80 mmHg

Method

- Good outcome : CPC ≤ 2, mRS ≤ 3
- Initial neurologic examination without sedation within the first 6 h of ROSC was recorded using the FOUR score --- Motor, Brainstem, Respiratory, and Eye responses
- Organ system dysfunction by SOFA scale

Categories of initial post-arrest illness severity. FOUR, Full Outline of Unresponsiveness; SOFA, Serial Organ Function Assessment.

Category	FOUR motor + brainstem score	SOFA cardiovascular + respiratory score	Description
I	8	Any	Awake – follows commands
II	4–7	<4	Coma with preserved brainstem reflexes
III	4–7	≥4	Coma with preserved brainstem reflexes, and severe cardiopulmonary failure
IV	<4	Any	Coma with loss of some or all brainstem reflexes

- Category I excluded from the analyses.

Method

- Each vasopressor drug (epinephrine, norepinephrine, phenylephrine, dopamine, and vasopressin) and dosage was measured.
- Cumulative vasopressor index (CVI)
- CVI values were log-transformed for analysis as they were not normally distributed.
- dobutamine and milrinone, which were analyzed separately

Method

- temperature vs. time curve was fit and then the area under the curve was calculated to determine the dose of TH
- We assumed the relationship between temperature and time followed a smooth (cosine) curve so that the dose of TH is well known. (Monte Carlo simulation)
- Three doses were considered:

low (9 ◦C h), medium (18 ◦C h), and high (36 ◦C h)

Result

Demographic data. VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; OHCA, out of hospital cardiac arrest; MAP, mean arterial blood pressure; CVI, summative cardiovascular index.

	Hypothermia (N = 233)	Normothermia (N = 128)	p-Value
Age	58.5 (17)	64.4 (16)	0.001
Male	126 (54.1%)	64 (50%)	0.527
Rhythm			
VF/VT	98 (42.1%)	39 (30.5%)	
PEA	58 (24.9%)	49 (38.3%)	0.041
Asystole	48 (20.6%)	23 (18%)	
Unknown	29 (12.4%)	17 (13.3%)	
OHCA	175 (75.1%)	53 (41.4%)	<0.001
Category of arrest			
II	89 (38.2%)	29 (22.7%)	
III	35 (15%)	38 (29.7%)	<0.001
IV	109 (46.8%)	61 (44.7%)	
Initial 24 h (median, IQR)			
Fluid balance (mL)	−264 (−1337, 1242)	−72 (−1294, 562)	0.773
Median MAP (mmHg)	83 (75, 93)	79 (70, 86)	<0.001
CVI	2.5 (0, 43)	19.5 (0, 53)	0.072
Initial 36 h (median, IQR)			
Fluid balance (mL)	−188 (−1451, 1980)	−284 (−1170, 631)	0.717
MAP (mmHg)	82 (75, 89)	77 (70, 87)	0.005
CVI	7.5 (0, 68)	20.5 (0, 83)	0.168
Received CVI medication	108 (46.4%)	77 (60.2%)	0.016
Received dobutamine	30 (12.9%)	24 (18.8%)	0.179
Received milrinone	12 (5.2%)	8 (6.2%)	0.844
Dose of TH in hours (median, IQR)			
34 °C cutoff	10.1 (5, 16)	-	
35 °C cutoff	23.3 (13, 32)	-	
Survival	75 (32.2%)	45 (35.2%)	0.649
Length of stay (days)	10.5 (13.7)	12.8 (16.4)	0.176

Result

Rate of vasopressor, dobutamine and milrinone use by category of post-cardiac arrest illness. CVI Drugs – any drug in the cumulative vasopressor index.

	Hypothermia	Normothermia	p-Value
Category II	(n = 89)	(n = 29)	
CVI Drugs	29 (33%)	10 (35%)	0.85
Dobutamine	10 (11%)	3 (10%)	0.89
Milrinone	5 (6%)	0 (0%)	0.33
Category III	(n = 35)	(n = 38)	
CVI Drugs	18 (51%)	29 (76%)	0.03
Dobutamine	3 (9%)	10 (26%)	0.05
Milrinone	1 (3%)	3 (8%)	0.62
Category IV	(n = 109)	(n = 61)	
CVI Drugs	61 (56%)	38 (62%)	0.42
Dobutamine	17 (16%)	11 (18%)	0.68
Milrinone	6 (6%)	6 (10%)	0.56

Predictors of total cardiovascular index shown as coefficients. Other inotrope-use of dobutamine or milrinone.

	Estimate (95% CI)	p
Dose below 34 °C	0.06 (−0.13, 0.25)	0.54
FOUR Motor	−0.19 (−0.49, 0.12)	0.22
FOUR Brainstem	−0.06 (−0.24, 0.11)	0.47
SOFA Respiratory	0.25 (0.04, 0.46)	0.02
SOFA Cardiac	0.08 (−0.12, 0.28)	0.42
Other inotrope	0.50 (−0.04, 1.03)	0.07
PEA	−0.61 (−1.29, 0.07)	0.08
Asystole	−0.40 (−1.20, 0.39)	0.31
Unknown	−0.60 (−1.51, 0.30)	0.19
Dose below 35 °C	0.08 (−0.11, 0.27)	0.40
FOUR Motor	−0.19 (−0.49, 0.12)	0.22
FOUR Brainstem	−0.07 (−0.25, 0.11)	0.45
SOFA Respiratory	0.24 (0.04, 0.45)	0.02
SOFA Cardiac	0.09 (−0.11, 0.29)	0.37
Other inotrope	0.51 (−0.02, 1.04)	0.06
PEA	−0.65 (−1.32, 0.03)	0.06
Asystole	−0.46 (−1.27, 0.35)	0.26
Unknown	−0.63 (−1.53, 0.28)	0.17

	Odds Ratio (95% CI)	p
Survival		
Dose below 34 °C	0.95 (0.65, 1.37)	0.78
FOUR Motor	2.50 (1.56, 4.19)	<0.001
FOUR Brainstem	1.81 (1.30, 2.63)	<0.001
SOFA Respiratory	0.71 (0.49, 1.01)	0.06
SOFA Cardiac	0.89 (0.60, 1.30)	0.56
OHCA	2.03 (0.57, 7.89)	0.29
PEA	0.26 (0.06, 1.06)	0.07
Asystole	1.08 (0.28, 4.20)	0.91
Unknown	0.42 (0.10, 1.70)	0.23
Dose below 35 °C	0.91 (0.62, 1.31)	0.60
FOUR Motor	2.49 (1.56, 4.18)	<0.001
FOUR Brainstem	1.82 (1.30, 2.65)	<0.001
SOFA Respiratory	0.72 (0.50, 1.01)	0.07
SOFA Cardiac	0.89 (0.60, 1.29)	0.53
OHCA	2.00 (0.56, 7.78)	0.30
PEA	0.27 (0.06, 1.11)	0.08
Asystole	1.14 (0.29, 4.55)	0.85
Unknown	0.44 (0.10, 1.85)	0.27

Discharge disposition		
Dose below 34 °C	0.90 (0.60, 1.32)	0.59
FOUR Motor	2.46 (1.45, 4.48)	<0.001
FOUR Brainstem	1.44 (0.99, 2.16)	0.07
SOFA Respiratory	0.83 (0.57, 1.18)	0.30
SOFA Cardiac	1.06 (0.69, 1.62)	0.78
OHCA	4.10 (0.83, 31.64)	0.11
PEA	0.13 (0.01, 0.81)	0.07
Asystole	0.74 (0.13, 3.41)	0.70
Unknown	0.80 (0.18, 3.27)	0.75
Dose below 35 °C	0.87 (0.59, 1.25)	0.45
FOUR Motor	2.47 (1.45, 4.48)	<0.001
FOUR Brainstem	1.45 (0.99, 2.17)	0.06
SOFA Respiratory	0.83 (0.58, 1.19)	0.31
SOFA Cardiac	1.05 (0.68, 1.60)	0.82
OHCA	3.98 (0.81, 30.68)	0.12
PEA	0.14 (0.01, 0.87)	0.07
Asystole	0.80 (0.14, 3.80)	0.78
Unknown	0.86 (0.19, 3.61)	0.84

CPC ≤ 2[a]		
Dose below 34 °C	2.02 (0.79, 6.31)	0.17
FOUR Motor	2.85 (0.94, 13.61)	0.11
SOFA Respiratory	0.87 (0.37, 1.97)	0.73
SOFA Cardiac	0.88 (0.19, 2.13)	0.81
OHCA	0.46 (0.04, 10.74)	0.54
Dose below 35 °C	1.98 (0.77, 6.76)	0.21
FOUR Motor	2.78 (0.93, 12.62)	0.11
SOFA Respiratory	0.88 (0.38, 1.96)	0.75
SOFA Cardiac	0.87 (0.20, 2.08)	0.79
OHCA	0.55 (0.05, 12.86)	0.64
mRS ≤ 3[a]		
Dose below 34 °C	1.36 (0.61, 3.31)	0.46
FOUR Motor	2.53 (0.95, 9.52)	0.10
SOFA Respiratory	0.81 (0.38, 1.63)	0.56
SOFA Cardiac	0.82 (0.18, 1.87)	0.70
OHCA	0.69 (0.08, 15.40)	0.76
Dose below 35 °C	1.22 (0.58, 2.99)	0.63
FOUR Motor	2.46 (0.94, 8.91)	0.10
SOFA Respiratory	0.82 (0.39, 1.63)	0.57
SOFA Cardiac	0.82 (0.19, 1.85)	0.70
OHCA	0.78 (0.09, 17.21)	0.84

Discussion

- subjects receiving TH were not more likely to require vasopressors following resuscitation from cardiac arrest
- category III subjects treated with TH received less vasopressors or dobutamine than their normothermic counterparts.(理論上此分類的心肺功能更差)
- The need for vasopressor or inotropic support should not be a contraindication to receiving TH.

Discussion

- hypothermia “dose” was not independently associated with total CVI dose in subjects receiving TH.
- The “dose” of hypothermia was not associated with either survival or good outcome.
- The optimal “dose” of TH is unknown.

Limitation

- Temperature data were recorded hourly and some data points were missing.
- these data were obtained before and after implementation of a comprehensive care plan. lacks the rigor of a controlled trial.
- these data explored only one range of TH “dose.” The optimal “dose” of TH after cardiac arrest remains unknown.
- the proportion of subjects receiving inotropic support in each category of post-cardiac arrest illness severity is small

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Resuscitation 84 (2013) 200–205

Contents lists available at SciVerse ScienceDirect

Resuscitation

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The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients☆

Sang Hoon Oh[a], Kyu Nam Park[a,*], Young Min Kim[a], Han Joon Kim[a], Chun Song Youn[a], Soo Hyun Kim[a], Seung Pill Choi[a], Seok Chan Kim[b], Young Min Shon[c]

[a] Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[b] Department of Respiratory and Critical Care Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[c] Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Introduction

- several electroencephalogram (EEG) features may significantly improve prognostication in these patients at an early phase
- cEEG monitoring requires experienced specialists for application and interpretation and is often unavailable
- Amplitude-integrated electroencephalograms (aEEGs) are generated from single- or two-channel EEG recordings, and the records they produce are notably easy to read

Method

- comatose survivors of cardiac arrest in the ED of Seoul St. Mary's Hospital
- This study was conducted from September 2010 to August 2011
- adult (age >19 years) patients
- Exclusion criteria included a known history of neurological diseases, such as epilepsy, cardiac arrest from spontaneous or traumatic brain injury, or early death within 72 h after cardiac arrest.

Method

- All patients were monitored with aEEG using a combined singlechannel aEEG/EEG digital device
- The recording continued until patients regained consciousness, patients died, or at least 72 h had passed since cardiac arrest.
- After treatment of the patient with a combination of antiepileptic drugs → conventional EEG was performed as soon as possible

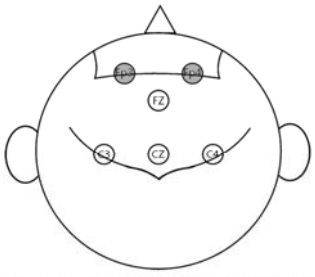
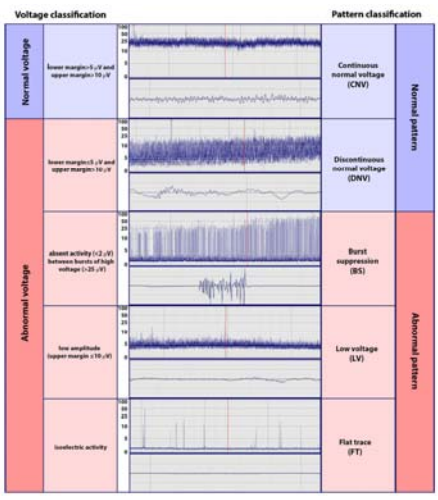


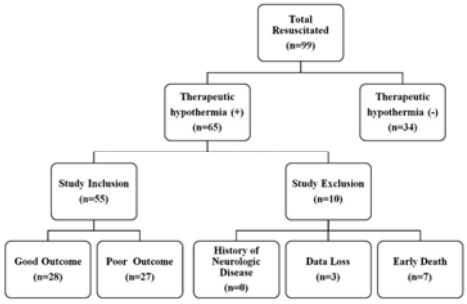
Fig. 1. The shaded electrodes are placed on the forehead for the single channel amplitude integrated electroencephalogram.



Method

- The aEEG recordings were interpreted by two board-certified neurologists
- Neurological outcome --- Cerebral Performance Categories (CPCs). Outcomes were dichotomised into good (CPC 1 and 2) and poor (CPC 3–5) outcomes.

Result



Result

Baseline demographics and clinical characteristics of good outcome and poor outcomes.

	Good outcome (n = 28)	Poor outcome (n = 27)	p-Value
Male, n (%)	17 (60.7)	16 (59.3)	0.912
Age, years	50.0 ± 18.4	49.9 ± 16.5	0.969
Witnessed, n (%)	21 (75.0)	18 (66.7)	0.562
Shockable rhythm, n (%)	14 (50.0)	6 (22.2)	0.050
Cardiac cause, n (%)	25 (89.3)	18 (66.7)	0.042
Time from arrest to ROSC, min	25.0 ± 13.5	40.7 ± 19.8	0.002
Time from ROSC to TH initiation, min*	0.0 (0.0–147.0)	0.0 (0.0–105.0)	0.926
Time from ROSC to aEEG apply, min*	84.0 (34.8–247.8)	97.0 (58.0–148.0)	0.873
Time from ROSC to initial aEEG detection, min*	99.5 (54.0–247.8)	145.0 (68.0–196.0)	0.584
Time from ROSC to target temperature, min*	150.0 (90.5–404.8)	170.0 (100.0–300.0)	0.602

Result

Sensitivity, specificity, positive and negative predictive value of initial aEEG for good outcome prediction.

	Good outcome group (n = 28)	Poor outcome group (n = 27)	Good outcome prediction			
			Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Voltage method						
Normal voltage	16	1	57.1 (37.2–75.5)	96.3 (81.0–99.9)	94.1 (71.3–99.9)	68.4 (51.4–82.5)
Abnormal voltage	12	26				
Pattern method						
Normal pattern	17	3	60.7 (40.6–78.5)	88.9 (70.8–97.7)	85.0 (62.1–96.8)	68.6 (50.7–83.2)
Abnormal pattern	11	24				

Sensitivity, specificity, positive and negative predictive value of aEEG within 72 h for poor outcome prediction.

	Poor outcome group (n = 27)	Good outcome group (n = 28)	Poor outcome prediction			
			Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Voltage method						
No developing normal voltage	21	0	77.8 (57.7–91.4)	100.0 (87.7–100.0)	100.0 (83.9–100.0)	82.4 (65.5–93.2)
Developing normal voltage	6	28				
Pattern method						
No developing normal pattern	17	0	63.0 (42.4–80.6)	100.0 (87.7–100.0)	100.0 (80.5–100.0)	73.7 (56.9–86.6)
Developing normal pattern	10	28				

Discussion

- CNV trace in aEEG is reliable to predict a good outcome in TH-treated patients
- no development of a CNV trace within 3 days was an accurate and reliable predictor of poor outcome.
- Amplitude criteria easily allow even non-neurologists to assess the severity of encephalopathy and to monitor for seizures.
- aEEG 缺點: 1. 無法定位 2. seizures or artefact 很難區分
- Initial aEEG 較慢得到 : due to artefacts associated with therapeutic interventions

Discussion

- the highest amplitudes in terms of intermittent cortical activity were recorded in the frontal leads, and continuous activity appeared first in the frontal leads.
- Mild hypothermia does not influence aEEG, and EEG is not significantly affected at a body temperature of 33 ◦C.
- Benzodiazepines have been described to increase frequency but do not decrease EEG amplitude in frontal brain areas.

Limitation

1. the sample size is relatively small for estimating the outcome or prevalence of patients with each aEEG pattern.
2. physicians were not blinded to the aEEG data during treatment.
3. many artefacts that needed to be controlled were identified in patient cohorts.
4. we used the discharge CPC instead of the long-term outcome for outcome assessment.