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Clinical paper

The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome☆

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ABSTRACT

Background: The incidence of shivering in cardiac arrest survivors who undergo therapeutic hypothermia (TH) is varied. Its occurrence is dependent on the integrity of multiple peripheral and central neurologic pathways. We hypothesized that cardiac arrest survivors who develop shivering while undergoing TH are more likely to have intact central neurologic pathways and thus have better neurologic outcome as compared to those who do not develop shivering during TH.

Methods: Prospectively collected data on consecutive adult patients admitted to a tertiary center from 1/1/2007 to 11/1/2010 that survived a cardiac arrest and underwent TH were retrospectively analyzed. Patients who developed shivering during the cooling phase of TH formed the "shivering" group and those that did not formed the "non-shivering" group. The primary end-point: Pittsburgh Cerebral Performance Category (CPC) scale; good (CPC 1–2) or poor (CPC 3–5) neurological outcome prior to discharge from hospital.

Results: Of the 129 cardiac arrest survivors who underwent TH, 34/94 (36%) patients in the "non-shivering" group as compared to 21/35 (60%) patients in the "shivering" group had good neurologic outcome ($P = 0.02$). After adjusting for confounders using binary logistic regression, occurrence of shivering (OR: 2.71, 95% CI 1.099–7.41, $P = 0.04$), time to return of spontaneous circulation (OR: 0.96, 95% CI 0.93–0.98, $P = 0.004$) and initial presenting rhythm (OR: 4.0, 95% CI 1.63–10.0, $P = 0.002$) were independent predictors of neurologic outcome.

Conclusion: The occurrence of shivering in cardiac arrest survivors who undergo TH is associated with an increased likelihood of good neurologic outcome as compared to its absence.

1. Introduction

The use of mild therapeutic hypothermia (TH) has been shown to be associated with improved neurologic outcome when used in patients successfully resuscitated from cardiac arrest.[1,2] However, the beneficial effect of TH in these patients is also dependent on other clinical factors and thus the outcome is varied in this population. For instance the rhythm leading to cardiac arrest, bystander cardiopulmonary resuscitation (CPR) and time to return of spontaneous circulation (ROSC) have been shown to predict outcomes in cardiac arrest survivors undergoing TH.[2–5] Thus, the prognostication of cardiac arrest survivors undergoing TH with regards to neurologic outcome remains challenging.

Shivering is a natural thermoregulatory response of the human body to cooling.[6] The occurrence of shivering during TH has been a concern since uncontrolled shivering during this therapy has been associated with longer time to achieve target cooling temperatures and thus may adversely affect outcomes in cardiac arrest survivors.[7] However, recent reports suggest that those patients who develop shivering during TH are more likely to have intact neurologic pathways and thus have better neurologic outcomes than those who do not.[8,9] Thus, we hypothesized that those cardiac arrest survivors who underwent TH and developed shivering are more likely to have better neurologic outcome than those who do not develop shivering during TH.

2. Methods

2.1. Study population

Consecutive adult patients who were admitted to the Cardiac Intensive Care Unit (CICU) at Hartford Hospital between January

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1, 2007 and November 1, 2010 after successful resuscitation from an out-of-hospital or in-hospital cardiac arrest and underwent TH formed the study cohort. The inclusion criteria were: an age of 18–75 years, Glasgow Coma Scale ≤ 8 after ROSC, an estimated interval of 5–15 min from the patient's collapse to the first attempt at resuscitation by emergency medical personnel, an interval of no more than 30 min from collapse to ROSC. Patients were excluded if they met any of the following criteria: missing key data, Glasgow Coma Scale > 8 after ROSC, a tympanic-membrane temperature below 30 °C on admission, response to verbal commands after the ROSC and before initiation of hypothermia, evidence of hypotension (mean arterial pressure less than 60 mmHg or systolic blood pressure less than 90 mm of Hg) for more than 30 min after the ROSC and before initiation of hypothermia, evidence of hypoxemia (arterial oxygen saturation, less than 85%) for more than 15 min after the ROSC and before initiation of hypothermia. Patients who were pregnant or had a terminal illness that preceded the arrest did not receive TH.

2.2. Study design and procedures

This was a retrospective study conducted on prospectively gathered data and was approved and conducted as per guidelines of the institutional review board at Hartford Hospital which also includes a formal ethical approval to conduct this study. Patients who formed the study cohort received TH and were admitted to the CICU after successful resuscitation from cardiac arrest. For purpose of the study, patients were grouped into the "non-shivering" and "shivering" groups respectively based on the occurrence of shivering during TH. Patients underwent TH with a goal to target temperature of 32–34 °C using a combination of an infusion of 2 L of cold normal saline at 4 °C administered via a central venous catheter during a period of 20–30 min with an intravenous pressure bag inflated to 300 mmHg, ice-packs and followed by use of an intracaval cooling device. Intracaval cooling was initiated as soon as feasible using an endovascular cooling catheter (ICY Catheter, ZOLL Temperature management, MA, USA) which was inserted into the right or left femoral vein in the CICU. The goal was to reach the target temperature within 4 h after return of spontaneous circulation. The target cooling temperature was defined as a core body temperature of 33 ± 1 °C. Hypothermia was maintained by endovascular cooling for 18 h and the patients were then re-warmed to a target temperature 37.0 °C set to a rate of 0.35 °C/h. Baseline vital signs, including temperature measured by rectal probe, were obtained before and during therapeutic hypothermia therapy. Temperature was measured every 15 min for the first hour followed by hourly measurements and blood pressure as well as heart rate were measured hourly throughout the CICU stay. Baseline laboratory tests included sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, hemoglobin, white blood cell count, platelet count, international normalized ratio (INR), lactic acid and arterial blood gases which were measured every 6 h after initiation of cooling with 4 °C normal saline infusion. Sedation (propofol, midazolam, lorazepam) was administered intravenously to all patients who underwent TH. Intravenous meperidine was used exclusively as treatment for shivering in patients as per hospital hypothermia protocol. Paralytic agent (atracurium, cistracurium, and vecuronium) was utilized either during intubation or only when shivering during TH could not be controlled using sedation or meperidine.

Patient data were obtained by querying the hospital TH database as well as systematic chart review of cardiac arrest patients admitted to Hartford Hospital during the study period. Data extracted also included location of arrest, time to ROSC, whether the arrest was witnessed, whether bystander cardiopulmonary resuscitation was provided and the initial presenting rhythm.

2.3. Evaluation of shivering

As per the TH protocol at Hartford Hospital, the occurrence of shivering during TH (including the rewarming phase) is documented by trained CICU nurses who are involved with the administration of TH. The episodes of shivering were differentiated from seizures by nursing staff, non-neurologist and neurologist physicians using clinical criteria. This differentiation was also supported when feasible by the use of electro-encephalography by a neurologist physician. We also cross-referenced the data on shivering obtained from the TH database with the documentation of administration of intravenous meperidine which is exclusively used as treatment for shivering as per the hospital TH protocol.

2.4. Evaluation of outcome

The endpoints of the study were either a good neurologic outcome, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a five category scale, or a poor neurologic outcome defined as Pittsburgh cerebral-performance categories 3 (severe disability), 4 (a vegetative state), and 5 (death) prior to discharge from the hospital.[10–12] The neurological evaluation of the patients was conducted by a consultant neurologist who examined the patient on a daily basis till discharge from hospital or till death.

2.5. Statistical analysis

Continuous variables which did not have a normal distribution were expressed as median and interquartile range. Medians were evaluated for significant differences using the Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages which were analyzed using the chi-square or Fisher exact test. Cumulative survival curves were obtained using the Kaplan–Meier procedure and compared using the log-rank test.

A multivariable analysis using binomial logistic regression was performed to determine the association of therapeutic hypothermia to good and poor neurologic outcomes as two separate end-points. Significant parameters obtained on univariable analysis as well as clinically significant variables with a $P < 0.20$ were entered into the logistic regression model.

A forward stepwise selection procedure, based on the Wald statistic probability, was performed, with a threshold of $P \leq 0.05$ and $P \geq 0.1$ for variable entry and removal, respectively. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the model. Goodness of fit was evaluated using the Hosmer–Lemeshow test. A reasonable fit can be assumed if the result has a *P* value > 0.05.

In all statistical analyses, a $P < 0.05$ was considered significant. All statistical analyses were two-tailed and were performed using SPSS version 17.0 software (SPSS, Chicago, IL).

3. Results

The demographics and clinical characteristics of the study cohort are shown in Table 1. Overall the two groups were relatively similar except for male gender and time to reach target hypothermia. There were significantly more number of males in the "shivering" group as compared to the "non-shivering" group (96% vs. 83% respectively, $P = 0.02$). The time to reach target hypothermia was significantly more in the "shivering" group as compared to the "non-shivering" group (360 min vs. 273 min respectively, $P = 0.02$). More patients in the "shivering" group received paralytic agents as compared to "non-shivering" group (66% vs. 39% respectively,