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Clinical paper

Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management☆

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ABSTRACT

Introduction: Time to achieve target temperature varies substantially for patients who undergo targeted temperature management (TTM) after cardiac arrest. The association between arrival at target temperature and neurologic outcome is poorly understood. We hypothesized that shorter time from initiation of cooling to target temperature ("induction") will be associated with worse neurologic outcome, reflecting more profound underlying brain injury and impaired thermoregulatory control.
Methods: This was a multicenter retrospective study analyzing data from the Penn Alliance for Therapeutic Hypothermia (PATH) Registry. We examined the association between time from arrest to return of spontaneous circulation (ROSC) ("downtime"), ROSC to initiation of TTM ("pre-induction") and "induction" with cerebral performance category (CPC).
Results: A total of 321 patients were analyzed, of whom 30.8% (99/321) had a good neurologic outcome. Downtime for survivors with good outcome was 11 (IQR 6–27) min vs. 21 (IQR 10–36) min ($p = 0.002$) for those with poor outcome. Pre-induction did not vary between good and poor outcomes (98 (IQR 36–230) min vs. 114 (IQR 34–260) ($p = \text{ns}$)). Induction time in the good outcome cohort was 237 (IQR 142–361) min compared to 180 (IQR 100–276) min ($p = 0.004$). Patients were categorized by induction time (<120 min, 120–300 min, >300 min). Using multivariable logistic regression adjusted for age, initial rhythm, and downtime, induction time >300 min was associated with good neurologic outcome when compared to those with an induction time <120 min.
Conclusion: In this multicenter cohort of post-arrest TTM patients, shorter induction time was associated with poor neurologic outcome.

1. Introduction

The implementation targeted temperature management (TTM) has resulted in improved neurologic outcomes and increased survival for patients suffering from post-cardiac arrest syndrome (PCAS).[1,2] The mechanism for such neurologic protection is thought to be multifactorial, including limitation of post-arrest endothelial dysfunction, decreased free radical production, and blunting of the post-reperfusion inflammatory cascade.[3] However, significant variation in patient outcomes when treated with TTM raises fundamental questions with regard to enrollment of patients in TTM protocols, neuroprognostication, and accurate identification of those individuals who will return to their pre-arrest neurologic state versus those who will remain neurologically devastated.

In animal models, reducing time from successful resuscitation to arrival at target temperature has shown improved neurologic outcome,[4] but evidence to corroborate these findings in human patients is mixed.[5–8] Early initiation of TTM has been the mainstay of post-arrest treatment to maximize neuroprotection.[9] In clinical practice, wide variability in the time to initiate TTM exists.[6–8,10]

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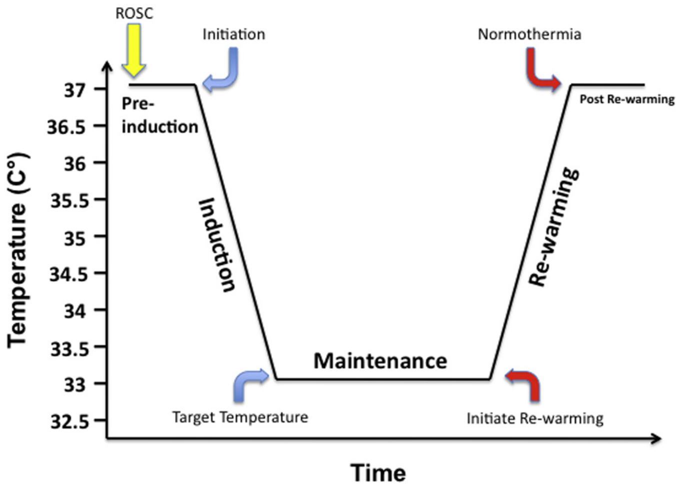

Fig. 1. The phases of targeted temperature management (TTM) in post cardiac arrest syndrome. A schematic diagram depicting the first 72 h post return of spontaneous circulation (assuming a starting temperature of normothermia and a maintenance temperature of 33 °C).

Despite protocolized management, substantial variability exists in the time from initiation of TTM to arrival at target temperature ("induction time") (Fig. 1). In contrast to animal studies, which are performed in a highly controlled fashion, clinical investigators have observed that precipitous achievement of target temperature may be associated with poor neurologic outcomes,[8] perhaps illustrating the complex relationship between injury, early neurologic damage, and patient thermoregulatory control post-arrest. Given that target temperature is static, and cooling devices are programmed to rapidly cool patients to a pre-specified target temperature, variability in time to target temperature is theorized to be secondary to the heat generation produced by the post-arrest patient.

Significant variability in pre-induction and induction time has been observed in post arrest patients treated with TTM. The primary objectives of this study were to examine the relationship between the length of the pre-induction and induction phases of TTM and neurologic outcome. We hypothesized that: (1) Individuals with shorter pre-induction times will survive with better neurologic outcomes as measured by Cerebral Performance Category (CPC). (2) Individuals who suffer greater neurologic injury during their cardiac arrest may exhibit loss of thermoregulatory control and lack of heat generation, resulting in shorter induction times and poor neurologic outcome as measured by CPC.

2. Methods

2.1. Study design and setting

The Penn Alliance for Therapeutic Hypothermia (PATH) Registry was created in 2010 as a national, on-line repository for patient data from multiple centers performing TTM. Data were utilized from two institutions that utilize the same TTM protocol and supply data to PATH: A large urban, level-1 trauma center, and an academic community affiliate. This study was approved by the University of Pennsylvania Institutional Review Board.

2.2. Study subjects and TTM protocols

Patients were considered for inclusion if they were: older than 18 years of age; suffered an in-hospital or out-of-hospital non-traumatic cardiac arrest due to any arrest rhythm; had return of spontaneous circulation (ROSC); remained comatose after arrest; and were treated with TTM (with a goal temperature of 33 °C). According to protocol, patients were considered for TTM if they were pulseless for less than 60 min and had a Glasgow Coma Motor Score (GMS) of less than 6 after ROSC. Patients were not eligible for TTM if they had evidence of intracranial hemorrhage or bleeding as the etiology of arrest or an active "Do Not Resuscitate" (DNR) order. After inclusion in the study, patients were excluded from analysis if they had withdrawal of life sustaining therapy or TTM withdrawn prior to arrival at goal temperature.

After the decision to initiate TTM was made, care administered during the induction phase was performed based on shared protocols at the two institutions. Cooling was initiated with 1–2 l of chilled normal saline infused through peripheral intravenous cannulae and placement of external fluid filled wraps connected to a thermostatically-controlled cooling unit (Meditherm III, Stryker, Kalamazoo, MI). Patient temperatures were recorded via either an esophageal or bladder catheter probe. TTM was initiated either in the Emergency Department, Cardiac Catheterization Laboratory or Intensive Care Unit. Further details of the TTM protocols employed at these two institutions have been published elsewhere (www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml).[11]

2.3. Data collection

Descriptive data were obtained for each subject, including age at arrest, sex, race, and body mass index (BMI, calculated using measured height and weight at the time of intensive care unit admission). Arrest characteristics, including year, initial rhythm, and "downtime" (time from cardiac arrest to when return of pulse was achieved) were abstracted from the medical record and recorded within the PATH database by trained research assistants at the two participating institutions. Specific time intervals measured include the pre-induction phase and the induction phase (Fig. 1). The primary outcome was neurologic status at hospital discharge recorded as CPC, dichotomized into "good" (CPC 1–2) and "poor" (CPC 3–5) outcomes.[12–14] Prior work has demonstrated that discharge CPC correlates well with longer-term outcomes.[15]

2.4. Statistical analysis

Demographic data and arrest characteristics were examined using summary statistics, and comparisons were made using chi-square and Student's *t*-tests (Table 1). Median downtime, pre-induction time and induction times were compared for patients with a "good" and "poor" neurologic outcome via Mann–Whitney *U* analysis for non-parametric data (Table 2). Demographic and arrest characteristics were analyzed using univariate logistic analysis to determine association with neurologic outcome. A Kaplan–Meier (KM) plot was created to illustrate the unadjusted induction time for patients with a "good" versus "poor" neurologic outcome, and a log-rank test was utilized to test the hypothesis that the KM curves were different (Fig. 2).

Induction time was categorized into three groups by analyzing the cohort as a whole. Patients were divided into the following categories: (1) <120 min, (2) 120–300 min and (3) >300 min. Groups 1 and 3 contain patients with induction time in the respective outlying quartiles, intended to represent extremes in induction time with group 1 cooling more rapidly and group 3 cooling over a longer duration of time. Multivariable logistic regression was employed to assess the association between induction time categories and poor neurologic outcome adjusting for relevant covariates as determined by the previous univariate analysis. Standard statistical software (Stata v. 12.1., Statacorp, College Station, TX) was used to analyze the data. Statistical significance was set at $p < 0.05$.