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Clinical paper

Relationship between timing of cooling and outcomes in adult comatose cardiac arrest patients treated with targeted temperature management☆,☆☆

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ABSTRACT

Aim of the study: Studies examining associations between time to target temperature and outcomes in cardiac arrest patients who underwent targeted temperature management (TTM) have shown inconsistent results. We examined these associations separately for time from restoration of spontaneous circulation to TTM initiation (pre-induction time) and time from TTM initiation to target temperature (induction time). Furthermore, we examined whether critical time thresholds exist if there is an association.
Methods: This was a single-centre retrospective observational study including adult cardiac arrest patients treated with TTM from 2008 to 2015. We tested the associations of pre-induction time and induction time with outcomes at hospital discharge using multivariate logistic regression analysis. We then performed additional multivariate analyses, each with the significant timing variable at different binary cutoffs.
Results: A total of 515 patients were analysed. At hospital discharge, 357 patients (69.3%) were alive, of whom 161 (31.3%) had a favourable neurologic outcome. In multivariate analysis, a shorter pre-induction time was independently associated with a favourable neurologic outcome (odds ratio [OR], 1.110; 95% confidence interval [CI], 1.025–1.202), whereas the induction time was not (OR, 0.954; 95% CI, 0.852–1.067). We found two pre-induction time thresholds (120 and 360 min) that were associated with neurologic outcome.
Conclusion: We found that a shorter pre-induction time was independently associated with a favorable neurologic outcome at hospital discharge, whereas induction time was not. We also found two time thresholds at 120 and 360 min, after which initiation of cooling was associated with a worse neurologic outcome.

Introduction

Targeted temperature management (TTM) has been widely recommended for the treatment of comatose cardiac arrest survivors since the publication of two landmark papers on therapeutic hypothermia.[1,2] Despite a number of studies regarding the TTM after cardiac arrest, many questions remain unanswered. Among them, the relationship between timing of cooling and outcome is an unresolved issue that bears important clinical implications. Animal studies have consistently shown that earlier cooling results in greater benefits from this therapy.[3–5] However, human studies have shown inconsistent results on the impact of earlier cooling.[6–14]

It appears reasonable to examine the association between time to target temperature, which is the time interval from restoration

Abbreviations: TTM, targeted temperature management; ROSC, restoration of spontaneous circulation; CNUH, Chonnam national university hospital; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; GCS, Glasgow coma scale; SOFA, sequential organ failure assessment; CPC, Cerebral Performance Categories; OR, odds ratio; CI, confidence interval.

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of spontaneous circulation (ROSC) to achievement of target temperature, and outcomes in order to understand how the timing of cooling impacts outcomes of comatose cardiac arrest survivors. The time to target temperature can be divided into two time intervals: pre-induction time, which is the time interval from ROSC to TTM initiation, and induction time, the time interval from TTM initiation to achievement of target temperature. According to the animal studies showing benefits of earlier cooling, a shorter pre-induction time is expected to be associated with favourable outcomes.[3–5] In contrast, clinical studies suggest that a shorter induction time is associated with worse outcomes.[11,14] Thus, regarding the pre-induction time and induction time, the associations with outcomes can be in the opposite direction, and the direction and significance of the association between time to target temperature and outcomes may vary depending on the relative contribution of the two time intervals to outcomes, thus resulting in inconsistent results in human studies.

In light of this, it may be more reasonable to distinguish between pre-induction time and induction time in exploring the association between the timing of cooling and outcomes. To our knowledge, few studies examined this association separately for the pre-induction and induction times.[11,14] In the present study, we sought to examine the associations of pre-induction time and induction time with survival to hospital discharge and neurologic outcome at hospital discharge. Furthermore, we sought to examine whether critical time thresholds exist if there is an association. We hypothesised that a shorter pre-induction time would be associated with favourable outcomes while a shorter induction time would be associated with unfavourable outcomes.

Methods

Study design and population

This was a retrospective observational cohort study of adult comatose cardiac arrest survivors treated with TTM at Chonnam National University Hospital (CNUH) in Gwangju, Korea, from January 2008 to December 2015. The Institutional Review Board of CNUH approved this study.

Cardiac arrest patients over 18 years of age who underwent TTM were included. Patients were excluded if (1) TTM was interrupted owing to transfer to another facility or haemodynamic instability, (2) they died before the target temperature was reached, (3) they were treated with a different TTM protocol, or (4) extracorporeal membrane oxygenation was applied during post-cardiac arrest care.

TTM protocol

No cooling attempt was made in the pre-hospital phase, and thus TTM was started after arrival at our hospital in all patients of this study. According to our protocol, TTM was considered for all nontraumatic cardiac arrest survivors who could not obey commands. Patients were not eligible for TTM if they had intracranial haemorrhage, active bleeding, known terminal illness, or a poor pre-arrest neurologic status. Cooling was initiated as soon as possible with ice packs, intravenous cold saline, and one of the following three TTM devices: Arctic Sun® Energy Transfer Pads™ (Medivance Corp, Louisville, KY, USA); Blanketrol® II (Cincinnati Subzero Products, Cincinnati, OH, USA); or COOLGARD3000® Thermal Regulation System (Alsius Corporation, Irvine, CA, USA). The target temperature of 33 °C was achieved and then maintained for 24 h using one of the TTM devices. Upon completion of the 24-h maintenance phase, active rewarming was attempted at a target rate of 0.25 °C–0.5 °C h^{-1} until the body temperature reached 36–36.5 °C. All patients undergoing TTM received continuous intravenous midazolam and remifentanil (or fentanyl) until at least 72 h after cardiac arrest. A neuromuscular blocking agent was administered to control shivering on an as-needed basis. All other aspects of patient management were at the discretion of the treating physicians.

Data collection

The following data were obtained from hospital records: age, sex, comorbidities, first monitored rhythm, aetiology of cardiac arrest, location of cardiac arrest, presence of a witness on collapse, bystander cardiopulmonary resuscitation (CPR), time to ROSC, transfer status (initially presented at CNUH versus initially presented at another hospital and transferred to CNUH), Glasgow Coma Scale (GCS) score after ROSC, initial temperature (recorded on hospital admission), TTM device, pre-induction time, induction time, duration of rewarming, sequential organ failure assessment (SOFA) score within the first 24 h after admission,[15] vital status at hospital discharge (alive or dead), and neurologic outcome at hospital discharge. For the calculation of pre-induction and induction times, the initiation of TTM was defined as the time when the first attempt of cooling was made. Neurologic outcome was assessed using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC) scale at discharge and recorded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death).[16] The primary outcome was an unfavourable neurological outcome, defined as CPC 3–5 at hospital discharge. The secondary outcome was in-hospital mortality.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Comparisons of categorical variables were performed using χ^2 or Fisher exact tests, as appropriate. Continuous variables were presented as median values with interquartile ranges because all continuous variables showed non-normal distribution. The Mann–Whitney *U* test was conducted for comparisons of continuous variables. The Kruskal–Wallis test was performed to compare induction times among the cooling devices. General linear model analysis was performed to identify the interaction between transfer status and location of cardiac arrest. Multivariate logistic regression analysis was used to examine the association between the timing of cooling and outcomes after adjusting for potential confounders. All variables with $p < 0.2$ in univariate analyses were included in the multivariate regression model. The multicollinearity between variables was assessed before modelling. Backward selection was used to obtain the final model. First, we entered the timing variables into the model as continuous variables. Second, to examine whether a significant time threshold value could be determined, we performed additional multivariate logistic regression analyses, each with the significant timing variable at different binary cutoffs (60-min increments from 60 to 420 min of pre-induction time). Data were analysed using PASW/SPSS™ software, version 18 (IBM Inc., Chicago, IL, USA). A two-sided significance level of 0.05 was used for statistical significance.

Results

A total of 636 adult cardiac arrest patients were treated with TTM during the study period. Of these, 121 patients were excluded as shown in Fig. 1. Thus, 515 patients were included in this study.

At hospital discharge, 357 patients (69.3%) were alive, of whom 161 (31.3%) had a favourable neurologic outcome. Clinical characteristics stratified by outcomes are shown in Table 1. Patients