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Clinical paper

Effect of therapeutic hypothermia on the outcomes after out-of-hospital cardiac arrest according to initial ECG rhythm and witnessed status: A nationwide observational interaction analysis☆

Sae Won Choi[a], Sang Do Shin[b,*], Young Sun Ro[c], Kyoung Jun Song[b], Eui Jung Lee[d], Ki Ok Ahn[c]

[a] Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Laboratory, Republic of Korea
[b] Department of Emergency Medicine, Seoul National University College of Medicine, Republic of Korea
[c] Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Republic of Korea
[d] Department of Emergency Medicine, Seoul National University Hospital, Republic of Korea

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ABSTRACT

Background: The use of mild therapeutic hypothermia (TH) in out-of-hospital cardiac arrest (OHCA) with shockable rhythms is recommended and widely used. However, it is unclear whether TH is associated with better outcomes in non-shockable rhythms.
Methods: This is a retrospective observational study using a national OHCA cohort database composed of emergency medical services (EMS) and hospital data. We included adult EMS-treated OHCA patients of presumed cardiac etiology who were admitted to the hospital during Jan. 2008 to Dec. 2013. Patients without hospital outcome data were excluded. The primary outcome was good neurological outcome at discharge; secondary outcome was survival to discharge. The primary exposure was TH. We compared outcomes between TH and non-TH groups using multivariable logistic regression, adjusting for individual and Utstein factors. Interactions of initial ECG rhythm and witnessed status on the effect of TH on outcomes were tested.
Results: There were 11,256 patients in the final analysis. TH was performed in 1703 patients (15.1%). Neurological outcome was better in TH (23.5%) than non-TH (15.0%) (Adjusted OR = 1.25, 95% CI 1.05–1.48). The effect of TH on the odds for good neurological outcome was highest in the witnessed PEA group (Adjusted OR = 3.91, 95% CI 1.87–8.14). Survival to discharge was significantly higher in the TH group (55.1%) than non-TH (35.9%) (Adjusted OR = 1.76, 95% CI 1.56–2.00).
Conclusions: In a nationwide observational study, TH is associated with better neurological outcome and higher survival to discharge. The effect of TH is greatest in witnessed OHCA patients with PEA as the initial ECG rhythm.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a public health problem worldwide. The American Heart Association estimates that about 424,000 emergency medical service (EMS)-assessed OHCA episodes, or 134 per 100,000 persons, occur each year in the United States.[1] The incidence of EMS-assessed OHCA is estimated to be 86 per 100,000 person-years in Europe, and 53 per 100,000 person-years in Asia.[2] OHCA is also associated with high morbidity and mortality, pooled data showing that approximately 23.8% of the patients survive to hospital admission but only 7.6% of the patients survive to hospital discharge.[3] The major cause of in-hospital mortality in patients who are resuscitated and survive to hospital admission is attributed to the post-cardiac arrest syndrome, composed of brain injury, myocardial dysfunction, systemic ischemia, and reperfusion response. Therapeutic hypothermia (TH) is a part of the recommended bundle of care that targets the post-cardiac arrest syndrome.[4]

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* Corresponding author at: Department of Emergency Medicine, Seoul National University College of Medicine, 101, Daehak-Ro Jongno-Gu, Seoul 110-744, Republic of Korea.
E-mail addresses: saewonchoi@gmail.com (S.W. Choi), shinsangdo@medimail.co.kr (S.D. Shin), Ro.youngsun@gmail.com (Y.S. Ro), skciva@gmail.com (K.J. Song), ironlyj@gmail.com (E.J. Lee), arendt75@gmail.com (K.O. Ahn).

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Two randomized controlled trials[5,6] published in 2002 demonstrated the survival benefit of TH in comatose OHCA patients due to ventricular fibrillation (VF), which led the International Liaison Committee on Resuscitation in 2003 to recommend TH to comatose adult survivors of VF OHCA.[7] However, a recent landmark study by Nielsen et al.[8] calls into question the benefit of induced hypothermia compared to maintaining normothermia in post-OHCA patients, showing that many questions on TH are still unresolved.[9] Nonetheless, TH is still widely used and the current guidelines recommend cooling comatose adult patients with return of spontaneous circulation (ROSC) to 32 °C to 34 °C for 12 to 24 h after VF OHCA (Class I, LOE B), and in-hospital cardiac arrest (IHCA) or after OHCA with an initial rhythm of pulseless electric activity (PEA) or asystole (Class IIb, LOE B).[9,10]

Numerous observational studies have confirmed the improvement in neurological outcomes and survival in OHCA with shockable initial rhythms.[11,12] However, the initial rhythm in the majority of OHCA is PEA/asystole,[2] and the guidelines support the use of TH in non-shockable rhythms while recognizing and emphasizing the need for further studies. There are no randomized controlled trials that directly test the benefit of TH in non-shockable rhythms, and results of observational studies have been conflicting. Recent meta-analysis of observational studies have shown an association with improved outcomes, but state that the quality of the evidence is poor.[13,14]

Further studies are needed to refine the details of TH, including the target population. In unwitnessed, non-shockable OHCA patients, it is debatable whether TH is associated with better outcomes. This study aimed to provide further evidence by comparing the effect of TH for the improvement of neurological outcome and survival to discharge in cardiac arrest patients, and the interaction effects of initial ECG rhythm and presence of witness on the effect of TH on outcomes.

Methods

Study setting and design

This is a retrospective observational study using a Korean national EMS-assessed OHCA cohort database, the Cardiovascular Disease Surveillance (CAVAS) project. The project started in 2006 and is sponsored by the National Emergency Management Agency and the Centers for Disease Control and Prevention of the Republic of Korea.[15–20] Data from EMS run sheets and hospital record reviews were used to form the database. Cases of OHCA were identified from the electronic EMS run sheets and medical record reviewers visited the hospitals to extract clinical information using structured forms based on the Utstein template. The reviewers were trained in data abstraction, used a standard manual, and consulted a quality assurance physician in equivocal cases.

The Korean EMS is a single tier system, based in fire stations, run by the fire department and provided for by the government. It serves a population of 50 million from 16 provincial headquarters with 1349 ambulances in 2010.[15] Prehospital providers are classified into level-1 and level-2 emergency medical technicians (EMT), comparable to EMT-intermediate and EMT-basic in the United States, respectively. International cardiopulmonary resuscitation (CPR) guidelines are endorsed by the Korean national organizations. The current EMS CPR protocol calls for EMTs to perform CPR, using an AED every 2 min, for at least 5 min or longer on scene. Intravenous fluid administration and advanced airway management may be optionally performed by level-1 EMTs. Epinephrine and other intravenous advanced cardiac life support (ACLS) medications are not available in the field. EMTs cannot declare death in the field unless there are signs of irreversible death (rigor mortis, dependent lividity, decapitation, transection and decomposition) and confirmed by direct medical control. If there is no ROSC after at least 5 min of CPR, EMTs transport the patients to the closest emergency department (ED) while continuing CPR during transport. Thus, almost all cases of OHCAs in Korea are transported to the closest ED. The government designates EDs into level 1 to 3 depending on the capability and capacity of the facility. Level 1 and level 2 EDs are fully staffed by emergency physicians by law. There are 20 level 1 EDs, 119 level 2 EDs, and 293 level 3 EDs as of December 2013 in Korea.[18,20] Although the recommendations of the national organizations are similar to the ones presented in the AHA and ERC guidelines, the TH protocol specifics on the method, equipment, timing, duration and temperature targets for induction, maintenance, and rewarming vary by hospital since they have yet to be established definitively.

Study population

Comatose patients who were 18 years and older with EMS-treated OHCA of presumed cardiac etiology admitted to the hospital after return of spontaneous circulation from January 2008 to December 2013 were included in the initial study population. We presumed the cause of arrest to be of cardiac etiology when there was no definite non-cardiac cause. A non-cardiac etiology was presumed if the medical record described the cause of death definitely as trauma, drowning, poisoning, burn, asphyxia, and hanging. Patients with unknown hospital outcome data were also excluded. Thus, comatose patients who survived to admission to the hospital intensive care unit were analyzed for this study.

Outcomes

The primary outcome of the study was hospital discharge with good neurological recovery, defined as a cerebral performance category (CPC) score 1 or 2. When the CPC score was not explicitly recorded in the medical record, medical record reviewers estimated the CPC score from information available in the medical or nursing record. Survival to hospital discharge was a secondary outcome.

Variables

The primary exposure, TH, was defined as a case receiving TH treatment using methods such as external cooling (water, fanning, or ice padding), internal cooling (gastric lavage, bladder cooling, or intravascular cooling using a catheter) or mixed cooling, with target temperature between 32 and 34 °C, and target duration of 12 to 24 h. A case was included in the hypothermia group if the hospital attempted the procedure but was withdrawn due to death during treatment regardless of the duration of treatment. On analysis, TH was classified as a binary variable, and did not take into account the equipment used; time and duration of induction, maintenance and rewarming; and target body temperature. We assessed for differences by year, age groups, gender, initial ECG rhythm (ventricular fibrillation/ventricular tachycardia (VF/VT), pulseless electrical activity (PEA), and asystole), community urbanization (rural or metropolis), ED level (levels 1, 2 and 3), presence of witness, place of arrest (public, private, and unknown), bystander CPR, defibrillation by EMS, EMS response time, EMS on scene time, EMS transport time, and prehospital ROSC. Data unavailable from medical records was regarded as 'unknown'; it was minimized by thorough medical record review of admitted patients. Furthermore, using an electronic database prevented skipped entries.

Statistical analysis

Descriptive statistics for categorical variables are presented as frequency distributions and percentages, and continuous variables