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Clinical Paper

The effect of mild therapeutic hypothermia on good neurological recovery after out-of-hospital cardiac arrest according to location of return of spontaneous circulation: A nationwide observational study☆

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ABSTRACT

Background: Mild therapeutic hypothermia (MTH) has been known to be associated with good neurological recovery after out-of-hospital cardiac arrest (OHCA). Prehospital return of spontaneous circulation (P-ROSC) is associated with better hospital outcomes than ROSC at emergency department (ED-ROSC). The study aims to examine the association between MTH by location of ROSC and good neurological recovery after OHCA.

Methods: Adult OHCA cases with presumed cardiac etiology who survived to hospital admission were collected from a nationwide cardiac registry between 2008 and 2013. MTH was defined as a case receiving hypothermia procedure regardless of procedure method. Primary outcome was good neurological recovery with cerebral performance category score of 1 and 2. Multivariable logistic regression analysis was performed adjusting for potential confounders with an interaction term between MTH and location of ROSC to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs).

Results: Among 11,158 patients survived to admission, good neurological recovery was 23.6% (399/1691) in MTH vs. 15.0% (1400/9316) in non-MTH ($p < 0.001$), and 58.2% (1074/1864) in P-ROSC vs. 7.9% (725/9161) in ED-ROSC ($p < 0.001$). There was a significant association between MTH and good neurological recovery (AOR = 1.32, 95% CI = 1.11–1.57). In the interaction model, AOR of MTH and interaction effect with P-ROSC and ED-ROSC was 0.78 (0.58–2.70) and 1.68 (1.34–1.98), respectively.

Conclusion: MTH was significantly associated with good neurological recovery among OHCA survivors. In the interaction model, MTH showed significant benefits in patient group with ROSC at ED, not in P-ROSC group.

1. Introduction

Out of hospital cardiac arrest (OHCA) is recognized as a worldwide, serious public health problem. The incidence of emergency medical services (EMS) treated OHCA was reported to be between 50 and 130 cases per 100,000.[1] In the US, only 9.8% of EMS-treated adult OHCAs survived to discharge from hospital.[2] In Korea, we have also reported that the incidence of EMS-assessed OHCA was approximately 45 per 100,000, and 3.5% of those patients survived to discharge from hospital.[3]

Previous studies have reported that factors such as witnessed arrest, initial shockable rhythm, bystander CPR, shorter EMS response time, use of public access defibrillator (PAD) program play a key role in survival to hospital discharge after OHCA.[4–6] Hospital interventions (i.e., post cardiac arrest care) comprised of targeted temperature management, optimal ventilation/oxygenation, optimizing hemodynamic parameter, seizure control, and electrolyte/glucose control have been developed to improve neurological outcome and survival of patients after cardiac arrest.[7]

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Over the past decades, researchers have found that hypothermia can decrease cerebral oxygen demand[8] and block chemical cascade leading to further cerebral injury.[9,10] Mild therapeutic hypothermia (MTH) is the core treatment that has demonstrated neurological benefits in comatose survivors with shockable cardiac arrest.[7,11–13] In 2002, two randomized trials have shown that hypothermia therapy in patients with initial shockable rhythm increased the rates of favorable neurological outcome One study enrolled adults OHCA patients who had ventricular fibrillation or ventricular tachycardia as initial rhythm and achieved ROSC within 60 min after cardiac arrest and reported MTH was significantly associated with more favorable neurological outcome at 6 month.[12] The other one also revealed that MTH gave OHCA patients with ventricular fibrillation as initial rhythm more chances to have good neurological outcome at discharge.[11] Moreover, even with the controversial debate over the effectiveness of hypothermia therapy, MTH still has possible neurological benefits in comatose adult OHCA patients with non-shockable rhythm.[14–17] As a result, MTH is incorporated as a part of standard post-cardiac arrest care.[7] Furthermore, in recent years, some researchers have verified that targeted temperature management (36 °C) without significant variation had similar effect on good neurological outcome compared with MTH.[18]

On the other hand, previous studies reported that prehospital ROSC (P-ROSC) is associated with more favorable neurological outcomes than ROSC at emergency department (ED-ROSC).[19–21] However, these studies did not account for the interaction effect between MTH and location of ROSC on favorable neurological outcome. We assumed that ischemic brain damage of OHCA patients resuscitated at ED is much greater than that of patients who ROSC at prehospital stage. Therefore, we hypothesized that the effect of MTH on neurological outcome could be different in patients depending on the location of ROSC. The purpose of this study was to investigate the effect of MTH on favorable neurological outcome in comatose adult patients after an out-of-hospital cardiac arrest according to the location of ROSC.

2. Methods

This study was approved by the Institutional Review Board of the Seoul National University Hospital in 2013 (No. 1206-007-412).

2.1. Data source

The Cardiovascular Disease Surveillance (CAVAS) database is a nationwide, population-based, EMS-assessed OHCA cohort database in Korea.[22] The primary data were accumulated from the electronic ambulance run sheet database of the National Emergency Management Agency (NEMA). Ambulance run sheets include chief complaints, sociological data, location of cardiac arrest, bystander cardiopulmonary resuscitation (CPR), time variables of resuscitation efforts, prehospital cares and the destination hospital information. Cases were coded as OHCA if the chief complaint was cardiac or respiratory arrest or if the patient received CPR during transport. Designated medical record reviewers of the Korea Centers for Disease Control and Prevention (CDC) collected secondary data for hospital outcomes and related information using customized Utstein style. The Data Quality Management Control (QMC) team composed of study co-investigators, statistics experts, medical record review experts, fire department managers and an epidemiologist conducted quality control activities.[3]

2.2. Study setting

Korea has a single-tier, basic life support (BLS) ambulance system operated by 16 provincial headquarters of the national fire department. Ambulance crews can give pre-hospital cares comparable to that of intermediate emergency medical technician (EMT-I) level in the US. However, advanced life support is only available in hospitals. The EMTs cannot declare death or stop CPR in the field or during transport unless ROSC occurs. Therefore, all patients with OHCA should be transported to the nearest ED. Public access defibrillator program was not available until 2008, so most defibrillation procedures in prehospital stage were given by ambulance crews. Every ambulance has an automatic external defibrillator. A withdrawal guideline for use in unsalvageable cases such as evidence of rigor mortis was included in the EMS act, but validity of such decision-making was not studied. Levels of hospital EDs are designated by the government based on capacity and resource availability such as facility, staffing, and devices. Level 1 EDs ($n = 20$) and level 2 EDs ($n = 110$) provide the highest level of emergency services by emergency medicine physicians for 24 h and 7 days. Level 3 EDs ($n = 310$) provide basic emergency care by general physicians. All EDs are subject to mandatory performance evaluation every year in keeping with public audit committee.[3] Hospital EDs generally accept international guidelines on acute cardiac care and resuscitation. However, no standard protocols for post-resuscitation care at hospitals care have been implemented.

2.3. Study subjects

We included all EMS-assessed OHCA patients who are 15 years of age or older with presumed cardiac cause and survived to hospital admission from January 1, 2008 to December 31, 2013 (6 years total). All cases were confirmed by medical record review. Patients who died prior to hospital admission as well as patients who had non-cardiac etiology (i.e., trauma, drowning, asphyxia, hanging or other obvious non-cardiac causes) were excluded. Furthermore, patients with unknown neurological status due to incomplete medical record were also excluded.

2.4. Study variables

We collected all potential confounders: sex, age, location of arrest, witnessed status, bystander CPR, residence in metropolitan (defined as population over 1 million), response time interval, scene time interval, transport time interval, initial electrocardiogram (ECG), pre-hospital defibrillation, level of ED, reperfusion therapy, and location of any ROSC (i.e., P-ROSC or ED-ROSC). Level of ED was divided into 3 groups according to the Korean Emergency Medical Service Act as regional emergency medical center, local emergency medical center, and local emergency medical facility. Reperfusion therapy included emergency coronary intervention, thrombolysis, and coronary artery bypass grafting (CABG).

2.5. Main exposure

MTH was defined as a case receiving mild therapeutic hypothermia 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. In standard, the target temperature should be between 32 and 34 °C and the minimum duration of hypothermia should be at least 12 h, but we regarded the case as part of the hypothermia-treated group if the hospital attempted the procedure regardless of the actual duration or early withdrawal of the procedure due to death during induced hypothermia. During the study period, hospitals had generally accepted 32–34 °C as the targeted temperature range in Korea.