Resuscitation xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Effect of target temperature management at 32–34 °C in cardiac arrest patients considering assessment by regional cerebral oxygen saturation: A multicenter retrospective cohort study

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ARTICLE INFO

Keywords:
Out-of-Hospital cardiac arrest
Resuscitation
Propensity score
Retrospective studies
Hypothermia
Induced
Spectroscopy
Near-Infrared

ABSTRACT

Aim: Target temperature management (TTM) is used in comatose post-cardiac arrest patients, but the recommended temperature range is wide. This study aimed to assess the effectiveness of TTM at 32–34 °C while considering the degree of cerebral injury and cerebral circulation, as assessed by regional cerebral oxygen saturation (rSO_2).

Methods: This is a secondary analysis of prospectively collected registry data from comatose patients who were transferred to 15 hospitals in Japan after out-of-hospital cardiac arrest (OHCA) from 2011 to 2013. The primary outcome was all-cause mortality at 90 days after OHCA, and the secondary outcome was favorable neurological outcomes as evaluated according to the Cerebral Performance Category. We monitored rSO_2 noninvasively with near-infrared spectroscopy, which could assess cerebral perfusion and the balance of oxygen delivery and uptake.

Results: We stratified 431 study patients into three groups according to rSO_2 on hospital arrival: $rSO_2 \leq 40\%$ (n = 296), rSO_2 41–60% (n = 67), and $rSO_2 \geq 61\%$ (n = 68). Propensity score analysis revealed that TTM at 32–34 °C decreased all-cause mortality in patients with rSO_2 41–60% (average treatment effect on treated [ATT] by propensity score matching [PSM] −0.51, 95%CI −0.70 to −0.33; ATT by inverse probability of treatment weighting [IPW] −0.52, 95%CI −0.71 to −0.34), and increased favorable neurological outcomes in patients with rSO_2 41–60% (ATT by PSM 0.50, 95%CI 0.32–0.68; ATT by IPW 0.52, 95%CI 0.35–0.69).

Conclusion: TTM at 32–34 °C effectively decreased all-cause mortality in comatose OHCA patients with rSO_2 41–60% on hospital arrival in Japan.

Introduction

Induced hypothermia, or target temperature management (TTM), has been used widely in clinical practice for comatose patients after cardiac arrest with return of spontaneous circulation (ROSC). TTM has become widespread after two randomized controlled trials (RCTs) were reported in 2002 [1,2]. Until 2010, international guidelines recommended induced hypothermia at 32–34 °C for 12–24 h for the treatment of comatose adult patients with ROSC after out-of-hospital cardiac arrest (OHCA) [3,4].

In 2013, a multicenter RCT by Nielsen et al. ("the TTM study") reported that TTM at 33 °C did not show superior effectiveness in terms of mortality and neurological outcomes compared to management at 36 °C in comatose OHCA patients [5]. This report had a large impact and spurred discussions, and differences in target populations among studies were also brought to attention. The condition of study subjects in Nielsen's TTM study were likely to be less severe compared to two previous trials [1,2] given differences in inclusion criteria and settings (control versus hypothermia, 48% versus 55% in mortality; 73% versus 49% in bystander cardiopulmonary resuscitation (CPR) rate) [6,7]. Furthermore, intensive care has evolved over the past decade, leading to improved patient care while possibly reducing the potential incremental benefits of a single intervention, such as hypothermia [7]. The recent guidelines modified the recommended temperature for TTM from 32 to 36 °C in 2015 [8].

Subsequent to the TTM study, several groups have studied TTM in various types of patients and failed to show its effectiveness. However, these previous studies did not focus on differences in the degree of

☆A Spanish translated version of the abstract of this article appears as Appendixi n the final online version at https://doi.org/10.1016/j.resuscitation.2018.02.007

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https://doi.org/10.1016/j.resuscitation.2018.02.007
Received 5 September 2017; Received in revised form 19 January 2018; Accepted 6 February 2018

cerebral injury of resuscitated patients. Although several useful measures to assess patient severity after admission to intensive care units exist [9,10], those useful upon hospital arrival have yet to be determined. In this regard, regional cerebral oxygen saturation (rSO_2) monitored in a noninvasive manner with near-infrared spectroscopy (NIRS), which could assess cerebral perfusion and delivery and uptake of oxygen, is potentially useful for the assessment of patients following cardiac arrest [11–13]. Therapeutic hypothermia reduces cerebral oxygen consumption [14,15] and suppresses cerebral reperfusion injury characterized by increased intracellular levels of glutamate and oxygen free-radical reactions [16,17] that occur upon restoration of cerebral blood flow after resuscitation. Against this backdrop, we hypothesized that the effectiveness of hypothermia would be modified by the degree of cerebral oxygen saturation, and that certain subgroups of unconscious resuscitated patients would benefit from this treatment.

This study aimed to examined the effectiveness of TTM at 32–34 °C while considering the degree of cerebral injury and cerebral circulation, as assessed by rSO_2 on hospital arrival.

Methods

Study design and data source

This was a secondary analysis of prospectively collected data from the Japan-Prediction of Neurological Outcomes in Patients Post-cardiac Arrest Registry [UMIN trial ID 000005065] [12,13], in which OHCA patients transported to 15 tertiary emergency hospitals in Japan from May 2011 to August 2013 were consecutively registered. The database consists of pre-hospital and in-hospital data collected from the Japanese emergency medical service (EMS) system and medical charts of each hospital by using the Utstein style [18]. All EMS providers in Japan are obligated to perform CPR according to the Emergency Life Guards Act [19]. Upon hospital arrival, all study patients received advanced life support in accordance with guidelines for resuscitation [3,4]. If sustained ROSC (at least 20 min) was not obtained, patients who initially showed electrocardiographic VF or pVT received extracorporeal CPR (ECPR).

Study population

Comatose patients after OHCA were included in this study if they achieved ROSC. Exclusion criteria were trauma, accidental hypothermia, age < 18 years, completion of "Do Not Resuscitate [20]" orders, and a Glasgow coma scale (GCS) score of > 8 on arrival at the hospital (Fig. 1).

After hospital arrival, two disposable probes for NIRS (INVOS TM 5100C, Covidien, Boulder, CO, USA) were attached to the patient's forehead. rSO_2 was monitored for at least 1 min after several seconds of stable monitoring, and the lowest rSO_2 value was used for the study [12,13].

Patients were stratified into three groups according to recorded rSO_2: group rSO_2 ≥61% (G1), group rSO_2 41–60% (G2), and group rSO_2 ≤40% (G3). These groupings were arrived at by referring to previous studies suggesting that values less than 35–40% or an absolute decrease of 20% from baseline should alert clinicians to perform appropriate interventions to reverse potential cerebral hypoxemia [21,22], and that rSO_2 values are 60% or higher in most stable patients [22,23]. We also conducted sensitivity analyses by changing these cut-offs for rSO_2 subgroups.

Variables

Treatment and outcome measurement

The treatment, i.e., TTM at 32–34 °C (12–24 h), was conducted by the discretion of the attending physician. Because the study was conducted using data from May 2011 to August 2013, results of the TTM study (published in November 2013) did not impact the present study. All procedural decisions regarding TTM (induction, maintenance, and weaning), use of ice-cold fluids or ice packs or surface temperature-management devices, sedation by midazolam and/or fentanyl, ventilator management, paralysis for preventing shivering, and evaluation and treatment of seizures, were based on the respective methods of each site and regimens reported from previous studies [1,2], and conformed to the 2010 American Heart Association guidelines [4].

We defined the primary outcome as all-cause mortality at 90 days after cardiac arrest, and the secondary outcome as favorable neurological outcomes evaluated according to the Cerebral Performance Category (CPC) [24]. The CPC is a 5-point scale ranging from 1 (good cerebral performance) to 5 (dead). We defined favorable neurological outcomes as 1 or 2 points on the CPC, in accordance with international guidelines [18,25]. Both all-cause mortality and neurological outcomes are core elements in the guidelines [18,25]. In principle, CPC in individual patients were determined by the physician-in-charge, but in cases of missing data, the main researcher who developed the database determined CPC by contacting patients or family members; both were blinded to rSO_2 readings.

Covariates

We used patient characteristics as covariates (Table 1), including demographic characteristics (sex, age), pre-hospital status (location of arrest, witnessed arrest, bystander CPR, first monitored rhythm), pre-hospital resuscitation attempts by EMS (airway management by intubation or laryngeal mask airway device, intravenous injection of adrenaline, usage of Automated External Defibrillator [AED]), patient

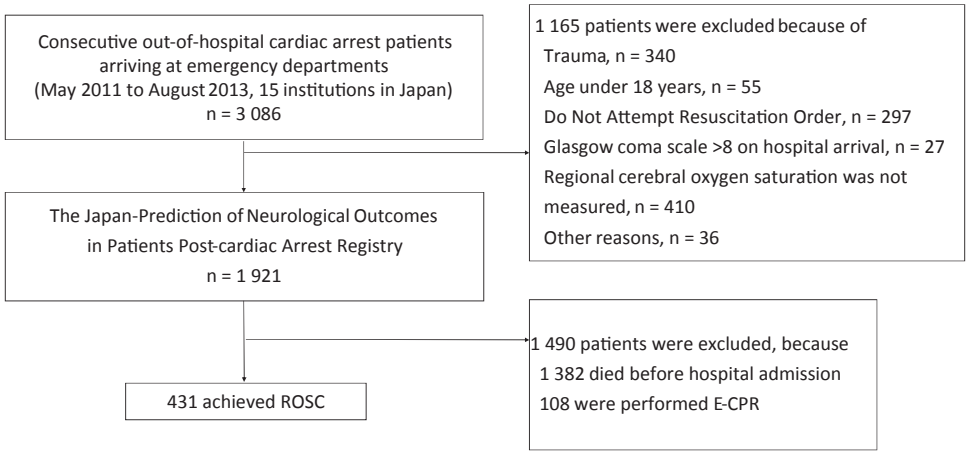

Fig. 1. Patient flowchart of 431 survivors of out-of-hospital cardiac arrest.