Effects of Targeted Temperature Management in Patients with Post-Cardiac Arrest Syndrome after an Out-Of-Hospital Cardiac Arrest Caused by Hanging: A Prospective Observational Cohort Study in Japan

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Abstract

Background: Targeted temperature management (TTM) is recommended for unconscious patients after a cardiac arrest. However, its effectiveness in patients with post-cardiac arrest syndrome (PCAS) by hanging remains unclear. Therefore, this study aimed to investigate the relationship between TTM and favorable neurological outcomes in patients with PCAS by hanging.

Methods: This study was a retrospective analysis of the Japanese Association for Acute Medicine out-of-hospital cardiac arrest (OHCA) registry between June 2014 and December 2017 among patients with PCAS admitted to the hospitals after an OHCA caused by hanging. A multivariate logistic regression analysis was performed to estimate the propensity score and to predict whether patients with PCAS by hanging receive TTM. We compared patients with PCAS by hanging who received TTM (TTM group) and those who did not (non-TTM group) using propensity score analysis.

Results: A total of 199 patients with PCAS by hanging were enrolled in this study. Among them, 43 were assigned to the TTM group and 156 to the non-TTM group. Logistic regression model adjusted for propensity score revealed that TTM was not associated with favorable neurological outcome at 1-month (adjusted odds ratio [OR]: 1.38, 95% confidence interval [CI]: 0.27–6.96). Moreover, no difference was observed in the propensity score-matched cohort (adjusted OR: 0.73, 95% CI: 0.10–4.71) and in the inverse probability of treatment weighting-matched cohort (adjusted OR: 0.63, 95% CI: 0.15–2.69).

Conclusions: TTM was not associated with increased favorable neurological outcomes at 1-month in patients with PCAS after OHCA by hanging.

Background

Suicide is a serious public health problem with mortality of >700,000 every year. In Japan, suicide is the leading cause of death among people aged 15–39 years. The majority of suicides are by hanging, and the incidence has been increasing over time. The prognosis for out-of-hospital cardiac arrest (OHCA) by hanging is extremely poor, and the neurological outcome for hanging survivors is also poor.

To improve the chance of neurological recovery, international guidelines recommended the use of targeted temperature management (TTM) for unconscious patients after cardiac arrest with any initial rhythm. Some reports suggested that TTM was effective in comatose patients induced by hanging to improve neurological outcomes, and TTM has been frequently performed in these patients. However, its effectiveness in post-cardiac arrest syndrome (PCAS) patients remains unclear. Therefore, this study aimed to investigate the relationship between the TTM and favorable neurological outcomes in patients with PCAS induced by hanging.

Methods

Design and setting
This was an observational study using data from the Japanese Association for Acute Medicine out-of-hospital cardiac arrest (JAAM-OHCA) registry, a nationwide hospital-based prospective observational data registry established in 2014 by the Registry Organizing Committee to improve treatment strategies, emergency care systems, and patient outcomes, between June 2014 and December 2017. Currently, 87 institutions are included in the registry; 66 of which are university hospitals and critical care centers. These critical care centers are accredited by the Ministry of Health, Labor, and Welfare and are equipped to provide highly specialized treatments, such as extracorporeal cardiopulmonary resuscitation, percutaneous coronary intervention, and TTM 24 h a day. The remaining 21 hospitals were not accredited as critical care centers but provided local emergency medical services. From June 2014 to December 2017, a total of 34,754 OHCA patients were enrolled in the JAAM-OHCA registry. This registry collected both pre- and post-hospitalization data, integrated by the JAAM-OHCA registry committee. Pre-hospitalization data were obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency. In-hospital data were collected by physicians or medical staff at each institution using an Internet-based system. The design and data collection methods for the JAAM-OHCA registry have been described previously. The registry was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (R-1045) and by each participating hospital. The use of data from the registry and retrospective analysis of anonymized data were approved by the Ethics Committee of Sapporo Medical University (312-3032).

Study participants

We included patients with PCAS admitted to the hospitals after an OHCA caused by hanging who were registered in the JAAM-OHCA registry between June 2014 and December 2017. Patients with missing pre- or in-hospital data were excluded.

Data collection

We collected and described the following clinical data from the JAAM-OHCA registry: sex, age, bystander performed cardiopulmonary resuscitation (CPR), an initial cardiac rhythm at the scene, prehospital intravenous line, prehospital epinephrine administration, prehospital airway management, prehospital return of spontaneous circulation (ROSC), time from call to ROSC, cardiac rhythm on arrival, Glasgow coma scale (GCS) on arrival, body temperature on arrival, epinephrine administration after arrival, and initial blood gas analysis after arrival.

Outcome measures

The outcome was favorable neurological status at 1-month after OHCA. The neurological outcome was assessed based on the Glasgow–Pittsburgh cerebral performance category (CPC) scale. The CPC scale is a five-category scale with the following categories: 1, good cerebral performance; 2, moderate cerebral disability; 3, severe cerebral disability; 4, coma or vegetative state; and 5, death or brain death. A favorable neurologic status was defined as a CPC scale of 1 or 2.
Statistical analysis

Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the chi-squared test or Fischer’s exact test. Propensity score analysis was performed to compare patients with PCAS by hanging who received TTM (TTM group) and those who did not (non-TTM group) using. Logistic regression analysis was performed to estimate propensity score and to predict whether patients with PCAS by hanging to receive TTM. Variables included in the model were age, sex, prehospital variables (bystander performed CPR, an initial cardiac rhythm at the scene, prehospital epinephrine administration, prehospital ROSC, and time from call to ROSC), in-hospital variables (cardiac rhythm on arrival, GCS on arrival, body temperature on arrival, and epinephrine administration after arrival), and arterial blood gas analysis (pH, partial pressure of carbon dioxide, base excess, and lactate level). In the unadjusted cohort, the individual propensity score was incorporated into the model as covariates, and propensity score-adjusted odds ratio (OR) was calculated using logistic regression analysis. Each patient in the TTM group patient was matched to a TTM group using nearest-neighbor matching without replacement. A caliper width equal to 0.25 of the standard deviation of the logit of the propensity score was used. The standardized mean difference was used to evaluate the covariate balance and a standardized difference of <0.1 represents a significant balance. Inverse probability of treatment weighting (IPTW) analysis was performed using propensity score-based weights, with trimming of the non-overlap regions to ensure that patients had a non-zero probability of receiving either treatment. Patients who received TTM were weighted using the inverse of the propensity score, whereas those who did not were weighted using the inverse of 1 minus the propensity score. Weights were stabilized to reduce the influence of extreme weights. ORs for the outcomes were estimated in the propensity score-matched and IPTW-matched cohorts. A two-sided $P$-value <0.05 was considered statistically significant for all tests. All analyses were performed using IBM SPSS software (version 24.0; IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

A total of 199 patients with PCAS by hanging were enrolled in this study. Among them, 43 were assigned to the TTM group and 156 to the non-TTM group (Figure 1).

Basic characteristics

The overall median age was 48 (interquartile range [IQR], 34–66) years, and age was significantly higher in the non-TTM group than that in the TTM group (50% vs. 41%, $p = 0.002$). The percentage of male patients was not different between the two groups. No difference in the initial rhythm was observed at the scene between the two groups, with asystole being the most common. The percentage of patients who had ROSC during transportation was not significantly different in both groups; however, time to ROSC from an emergency call was longer in the non-TTM group than that in the TTM group (33 min vs. 24 min, $p < 0.001$). The percentage of patients who had ROSC on arrival was 35.9% in the non-TTM group and 44.2% in the TTM group. The GCS on arrival was better in the non-TTM group than that in the TTM group.
Body temperature on arrival was lower in the non-TTM group than that in the TTM group (35.8°C vs. 36.1°C, p = 0.003). Regarding the blood gas analysis, a significant difference was observed in pH (6.86 vs. 6.96, p = 0.043), partial pressure of carbon dioxide (90.3 vs. 76.6, p = 0.022), and base excess (−19.6 vs. −15.9, p = 0.007) (Table 1).

**Propensity score analysis**

The propensity score matching created 34 pairs of patients who did or did not receive TTM. Table 1 shows the baseline characteristics of the original and propensity score-matched cohorts. In the matched population, the baseline characteristics of patients were almost balanced between the two groups. In contrast, IPTW using the propensity score-based weights did not fully reduce the imbalance for some covariates; however, these balance diagnostics we considered to be indicative of an adequate propensity score model (Figure 2).

Table 2 shows the association between TTM and favorable neurological outcomes at 1-month after OHCA. TTM was significantly associated with favorable neurological outcomes in the original cohort (unadjusted OR: 6.09, 95% confidence interval [CI]: 1.36–30.88; p = 0.008). However, the logistic regression model, adjusted for propensity score plus TTM, revealed that TTM was not associated with favorable neurological outcomes in the original cohort (adjusted OR: 1.38, 95% CI: 0.27–6.96; p = 0.7). Furthermore, no difference was observed in the propensity score-matched cohort (adjusted OR: 0.73, 95% CI: 0.10–4.71; p = 1.0) and in the IPTW-matched cohort (adjusted OR: 0.63, 95% CI: 0.15–2.69; p = 0.63).

**Discussion**

This study used nationwide, multicenter prospective OHCA registry data and revealed that TTM did not increase the favorable neurological outcomes of patients with PCAS after OHCA by hanging.

The survival rate at hospital discharge for patients with PCAS by hanging was significantly lower than that for patients with presumed cardiogenic cardiac arrest in the 10-year retrospective case review. A case report suggested that TTM may improve the outcomes of comatose patients after a cardiac arrest by hanging. However, recent studies reported that TTM was not associated with favorable neurological outcomes in patients with PCAS by hanging. A multicenter retrospective study reported that TTM worsened the unadjusted survival and neurological outcomes; however, the possibility of selection bias was suggested. To date, no randomized control trials have been conducted on TTM in patients with PCAS by hanging. The effectiveness of TTM for these patients is controversial. Our study supports the opinion that TTM does not improve the neurological outcomes in patients with PCAS by hanging.

The hypothesized pathophysiology of death by hanging is (1) asphyxia due to airway obstruction, (2) decreased cerebral blood flow due to cervical vascular occlusion, and (3) secondary cardiac inhibition due to vagal reflex. In these mechanisms, asphyxia due to airway obstruction was considered the principal mechanism of death through hanging. Asphyxial cardiac arrest is characterized by
progressive and global hypoxia with incomplete ischemia and results in gradually decreasing adenosine triphosphate depending on the length of asphyxia. Depletion of cellular energy starts the biochemical cascades that lead to cell damage and death before the cessation of cerebral blood flow\textsuperscript{15}. Therefore, the effectiveness of TTM for patients after a sudden cardiac arrest of cardiac origin has been proven, although its effectiveness for patients after cardiac arrest by hanging may be limited.

Previous studies have reported that mental status and GCS of >4 after ROSC are associated with favorable neurological outcomes\textsuperscript{12,16}. In this study, patients with a GCS of 3 after ROSC had favorable neurological outcomes regardless of whether they received TTM or not (Table 3). These patients had nearly normal arterial pH and mildly elevated lactate levels. Therefore, the possibility that comas were drug-induced rather than cardiac arrest-induced was considered. Furthermore, predicting the neurological outcomes based on the state of consciousness after a ROSC alone is difficult, and various factors should be considered.

This study has several limitations. First, although 34,754 OHCA patients were enrolled during the study period in the JAAM-OHCA registry, only 199 patients were included in this study. Therefore, when propensity score matching was performed, the number of patients in the two groups was even lower. However, we compensated for this limitation by performing multivariate logistic regression analysis adjusted for propensity score and by analyzing the IPTW-matched cohorts. Second, propensity score analysis was performed to simultaneously balance many covariates in the two groups and reduce the bias; however, the potential for unmeasured confounding remains. Third, we did not evaluate the TTM methods. Patient outcomes might have been affected by targeted temperature, duration of the maintenance phase, and rewarming rate. Finally, we could not evaluate the long-term neurological outcomes.

**Conclusions**

In patients with PCAS after OHCA by hanging, TTM was not associated with increased favorable neurological outcomes at 1-month.

**Abbreviations**

OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management; PCAS, post-cardiac arrest syndrome; JAAM, Japanese Association for Acute Medicine; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; GCS, Glasgow coma scale; CPC; cerebral performance category; OR, odds ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; CI, confidence interval

**Declarations**

Ethics approval and consent to participate
The registry was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (R-1045) and by each participating hospital. The use of data from the registry and retrospective analysis of anonymized data were approved by the Ethics Committee of Sapporo Medical University (312-3032). The need for informed consent was waived in view of the study design.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Not applicable.

**Authors' contributions**

RK: Conceptualization, Data curation, Formal analysis, Methodology, Writing - Original Draft. NB: Conceptualization, Methodology. SU: Methodology. TK: Investigation, Visualization. KS and HM: Writing - review and editing. EN: Supervision.

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Tables

Due to technical limitations, Tables are only available as a download in the Supplemental Files section.

Figures

Figure 1
Flowchart of the study population. OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, targeted temperature management

Figure 2

Standardized mean differences comparing before and after propensity score analysis. Standardized mean differences comparing before and after propensity score matching (left) and comparing before and after the inverse probability of treatment weighting (right). The dotted vertical line represents the standardized mean differences at 0.1. IPTW, inverse probability of treatment weighting; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; PaCO2, partial pressure of carbon dioxide.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.xlsx
- table2.xlsx
- table3.xlsx