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Clinical paper

A low body temperature on arrival at hospital following out-of-hospital-cardiac-arrest is associated with increased mortality in the TTM-study☆

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ABSTRACT

Aim: To investigate the association of temperature on arrival to hospital after out-of-hospital-cardiac arrest (OHCA) with the primary outcome of mortality, in the targeted temperature management (TTM) trial.

Methods: The TTM trial randomized 939 patients to TTM at 33 or 36 °C for 24 h. Patients were categorized according to their recorded body temperature on arrival and also categorized to groups of patients being actively cooled or passively rewarmed.

Results: OHCA patients having a temperature ≤34.0 °C on arrival at hospital had a significantly higher mortality compared to the OHCA patients with a higher temperature on arrival. A low body temperature on arrival was associated with a longer time to return of spontaneous circulation (ROSC) and duration of transport time to hospital. Patients who were actively cooled or passively rewarmed during the first 4 h had similar mortality.

In a multivariate logistic regression model mortality was significantly related to time from OHCA to ROSC, time from OHCA to advanced life support (ALS), age, sex and first registered rhythm. None of the temperature related variables (included the TTM-groups) were significantly related to mortality.

Conclusion: OHCA patients with a temperature ≤34.0 °C on arrival have a higher mortality than patients with a temperature ≥34.1 °C on arrival. A low temperature on arrival is associated with a long time to ROSC. Temperature changes and TTM-groups were not associated with mortality in a regression model.

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Introduction

Target temperature management with cooling after out of hospital cardiac arrest (OHCA) has been recommended since 2003,[1] after the publication of two trials indicating increased survival and improved neurological outcome in the hypothermia groups compared with no active temperature management control groups.[2,3] The evidence for the recommendation has been considered weak and new studies were suggested to address this problem.[4] The Target Temperature Management (TTM) trial published in 2013 demonstrated no difference in mortality and neurological outcome between a target temperature of 33 °C and 36 °C.[5] The result have been further elaborated in post-hoc and sub-studies on the data in the TTM-data base and have so far shown similar outcome in the two target temperature groups.[6–10]

The design of the TTM trial mandated that patients with an initial temperature below the target temperature to which they were randomized to, would gradually and passively be rewarmed to the target temperature. Patients with a body temperature close to their target temperature would experience small changes in their body temperature during the intervention stage. Possibly, an initial rewarming might have been harmful, and the rate of cooling might have been too slow to attain the presumed protection of hypothermia, as some detractors of the study have suggested.[11]

The spontaneous temperature trajectories after OHCA have not been studied in much detail in the OHCA population, however a lower body temperature on arrival and shorter times to reaching target temperature in patients who do not survive have been reported.[12–14] This post-hoc analysis was performed to investigate whether the body temperature on arrival was associated with the outcome in any of the two intervention groups.

Material and methods

Patients

This study is a post-hoc analysis of the TTM-trial, an investigator-initiated, multicentre, randomized, parallel group, and assessor-blinded clinical trial (NCT01020916).[5,15] The TTM-trial included adult patients (≥18 years) resuscitated from OHCA of presumed cardiac cause, irrespective of the initial rhythm, who remained unconscious (Glasgow coma scale <8) after sustained (>20 min) return of spontaneous circulation (ROSC). The main exclusion criteria were unwitnessed arrest with asystole as the primary rhythm, an interval from ROSC to screening of >240 min and a state of refractory shock, defined as a systolic blood pressure (SBP) of <80 mmHg despite fluid loading, vasopressors, inotropes and/or treatment with mechanical assist devices that could not be reversed within the inclusion time window.[5,15]

In the main study 950 patients were randomized, 11 patients were withdrawn.[5] Nine hundred and twenty six patients with recorded temperatures on arrival or at the start of the intervention were included in this post-hoc study. Patients were cooled by either surface cooling, by internal catheter-based methods, by cold intravascular fluids or by combinations thereof according to the practice in each participating site.

Patients in this post hoc analysis included those where valid data were available on temperature at arrival or at the start of the intervention. In 904 patients the temperature on arrival was recorded, in 22 patients the temperature at the start of the intervention was used as a surrogate for the initial temperature. In patients with both temperatures recorded there was no significant difference between the temperatures in a paired sample *T*-test Patients were recorded as cooled when temperature at the 4 h time-point was lower than the temperature on arrival and warmed when the temperature at 4 h was higher. The patients with identical temperature at arrival and after 4 h were defined as temperature neutral.

Patients were categorized in 2 groups according to their temperature on arrival or at the initiation of the temperature management period. One group had an initial temperature of 34.0 °C or below, the other group had an initial temperature of 34.1 °C or higher.

For some comparisons the patients were categorized into 5 groups based on the continuous variable of temperature on admission or at initiation of the temperature management A ($t \leq 34.0$ °C), B (34.1–35.0 °C), C (35.1–36.0 °C), D (36.1–37.0 °C) and E (≥37.1 °C)

Outcome

Primary outcome was mortality after 6 months as in the TTM trial, secondary outcomes were not included in this analysis.

Ethics

The TTM-trial is registered at ClinicalTrials.gov (NCT01020916) and the protocol was approved by ethical committees in each participating country. Informed consent was waived or obtained from all participants or their next of kin according to national legislation.

Statistical analysis

Approximately normally distributed continuous data are given by mean and confidence intervals (95%), not-normally distributed continuous data are represented with median and interquartile range (25–75%), binomial categorical data are presented as percentages with confidence intervals according to the method of Agresti and Coull as recommended by Lydersen, Fagerland and Laake.[16] Comparisons of binomial data were performed by Chi-square-test. Comparisons of normally distributed continuous data were performed by Student *T*-test, Kruskal–Wallis test was used for data that were not normally distributed.

The multivariate logistic regression analysis was performed with initial univariate analyses and inclusion of variables having a p value < 0.2 as recommended by Hosmer and Lemeshow.[17] The temperature variables were forced into the final model even without being significant in the univariate analysis, because our main focus was temperature in this work. We have not handled missing data by imputations, assuming the data were missing completely at random.

SPSS 21 was used for statistical analysis.

Results

The initial temperature or the temperature at the start of the intervention period was registered in 926 patients. The mean temperature on arrival was 35.2 °C as reported in the main publication. The mean temperature on arrival of those who were dead after 180 days was slightly lower than the temperature of those who survived (35.2 °C vs 35.3 °C, $p = 0.028$). There were 129 patients who had an arrival temperature of 34.0 °C or lower, 797 had an initial temperature higher than 34.1 °C. The proportion of patients having an initial temperature below 34.1 °C differed between the participating countries in the TTM-study (Table 1).

The patients who had a temperature of 34.0 °C or lower on arrival were dissimilar from the patients with higher temperatures as shown in Table 2. Spontaneously cold patients had a significantly higher proportion of unwitnessed OHCA, a longer time from CA to ROSC and a higher proportion of no-VT/VF reflecting unfavorable circumstances concerning the OHCA. This group of patients also had a significantly higher proportion of females, lower body weight and a longer time from CA to randomization. The proportion PCI undertaken was also higher in this group of patients.