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Clinical paper

Infectious complications after out-of-hospital cardiac arrest—A comparison between two target temperatures☆

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ABSTRACT

Background: It has been suggested that target temperature management (TTM) increases the probability of infectious complications after cardiac arrest. We aimed to compare the incidence of pneumonia, severe sepsis and septic shock after out-of-hospital cardiac arrest (OHCA) in patients with two target temperatures and to describe changes in biomarkers and possible mortality associated with these infectious complications.

Methods: Post-hoc analysis of the TTM-trial which randomized patients resuscitated from OHCA to a target temperature of 33 °C or 36 °C. Prospective data on infectious complications were recorded daily during the ICU-stay. Pneumonia, severe sepsis and septic shock were considered infectious complications. Procalcitonin (PCT) and C-reactive-protein (CRP) levels were measured at 24 h, 48 h and 72 h after cardiac arrest.

Results: There were 939 patients in the modified intention-to-treat population. Five-hundred patients (53%) developed pneumonia, severe sepsis or septic shock which was associated with mortality in multivariate analysis (Hazard ratio [HR] 1.39; 95%CI 1.13–1.70; p = 0.001). There was no statistically significant difference in the incidence of infectious complications between temperature groups (sub-distribution hazard ratio [SHR] 0.88; 95%CI 0.75–1.03; p = 0.12). PCT and CRP were significantly higher for patients with infections at all times (p < 0.001), but there was considerable overlap.

Conclusions: Patients who develop pneumonia, severe sepsis or septic shock after OHCA might have an increased mortality. A target temperature of 33 °C after OHCA was not associated with an increased risk

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of infectious complications compared to a target temperature of 36 °C. PCT and CRP are of limited value for diagnosing infectious complications after cardiac arrest.

Introduction

Infectious complications in intensive care impose a significant financial burden and are associated with increased morbidity and mortality.[1,2] Infection has been recognized as a complication following cardiac arrest[3] and it has been hypothesized that induced hypothermia increases infectious complications due to a reduction in humoral and cellular immunity,[3–6] although there is some inconsistency among studies.[7,8] Survivors of cardiac arrest also have a decreased ability to mount an adequate host response which puts them at risk of developing serious infections.[7]

Induced hypothermia hampers the diagnosis of pneumonia in several ways. Although a number of different diagnostic criteria for pneumonia exist, definitions usually include body temperature.[9,10] Furthermore, some of the commonly used infection biomarkers, including C-reactive protein (CRP) and the white blood cells (WBC) count might also be affected by hypothermia.[4,11–13] Making a reliable diagnosis of sepsis after cardiac arrest is also difficult for the same reasons. The fact that the post-resuscitation phase often mimics the clinical signs of sepsis is another confounder.[14]

Prior knowledge of risk factors for pneumonia after cardiac arrest is limited. Studies have shown that pneumonia is more common in patients treated with a target temperature of 33 °C,[3,5] although this did not reach significance in a previous randomized trial.[6] Results from a meta-analysis have not shown pneumonia and sepsis to be more common among patients treated with hypothermia.[15] Considering these conflicting results, there is uncertainty regarding the effect of temperature management on the incidence of infectious complications after cardiac arrest. It is also unclear whether infections have an impact on mortality. Prior studies have shown no difference in survival,[5,16] but they may have been affected by time-dependent bias.[17]

The randomized multi-center target temperature management after cardiac arrest trial (TTM-trial) showed no difference in the crude rate of infections between the 33 °C and 36 °C temperature groups.[18] As rates of infection are influenced by mortality, this comparison might be misleading. The present analysis investigates the incidence and timing of pneumonia and sepsis after cardiac arrest and describes changes in commonly used biomarkers. We used the modified intention-to-treat population of the TTM-trial to test the hypothesis that the rate of infectious complications differed between target temperature management at 33 °C and 36 °C. We also aimed to test if developing an infection after OHCA had an impact on mortality.

Methods

Patients

The present study is a post-hoc analysis of the multi-center, randomized, parallel-group, assessor-blinded TTM-trial.[18] The trial included adult (≥18 years) unconscious patients (Glasgow Coma Scale < 8) resuscitated from OHCA of a presumed cardiac cause with return of spontaneous circulation (ROSC) >20 min (sustained ROSC). Patients were included at 36 centers in Europe and Australia. In accordance with national requirements and the principles of the Declaration of Helsinki, written informed consent was waived, delayed, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity. Details on exclusion criteria, trial protocol and main results have previously been published.[18,19] Incidence of infections during day one to seven in the ICU has previously been reported in Appendix of the main publication.[18]

Post-cardiac arrest care and outcome

Patients were randomized to a target temperature of 33 °C or 36 °C with a total intervention period of 36 h. After the intervention patients were kept <37.5 °C until 72 h after cardiac arrest.[18,19] The primary outcome was death at the end of trial (180 days after the randomization of the last included patient).

Infectious complications

Data on clinical parameters and infectious complications were entered daily into an electronic case report form (eCRF) during the ICU-stay by the treating physician. The diagnosis of suspected pneumonia was based on presence of at least one of three clinical features (leucocytosis (>12,000 cells/μL), fever (>38 °C), and purulent tracheobronchial sections) in addition to a new or progressive consolidation visible on chest X-ray.[20,21] Due to temperature management no minimum number of criteria was specified for the diagnosis of pneumonia. Severe sepsis was defined as a suspected infection with two or more SIRS criteria (temperature >38 °C or <36 °C, a heart rate >90 beats/min, a respiratory rate >20 breaths/min or $Paco_2$ < 4.3 kPa, a white blood cell count >12,000 cells/μL or <4000 cells/μL, or >10% immature (band) forms) and hypoperfusion, hypotension or organ dysfunction. Septic shock was defined as severe sepsis with hypotension or the requirement for vasoactive drugs, despite adequate fluid resuscitation.[22,23] Other infections were based on clinical judgment and specified separately. If the local laboratory identified a causative microorganism the infection was considered confirmed. The diagnosis by the treating physician was considered final. Criteria for infection were provided as guides to the treating physician and not documented or confirmed by chart review.

All cases of confirmed and suspected pneumonia, severe sepsis and septic shock were considered infectious complications in the main analyses. As other infections were few, and not registered beyond day seven, they were not included.

Antibiotics were given according to local protocols, either as prophylactic/early treatment including selective digestive tract decontamination (SDD) or as guided treatment on a clinical indication. The treating physician made all decisions regarding antibiotics. All site-investigators were asked to specify their local protocols regarding use of prophylactic antibiotics and SDD.

Biomarkers

For a subset of patients (n = 700) at 29 centers participating in the biobank sub-study, serum samples were collected at 24 h, 48 h and 72 h after cardiac arrest as previously described.[24] Samples were stored in 500 μL aliquots at −80 °C at each study site. Samples were then shipped to the Integrated BioBank of Luxembourg. Determination of CRP was performed using a COBAS c601 line with a 3rd generation immunoturbidometric latex assay (Roche Diagnostics, Rotkreuz, Switzerland). PCT analyses were performed by