



Clinical paper

The biomarkers neuron-specific enolase and S100b measured the day following admission for severe accidental hypothermia have high predictive values for poor outcome[☆]



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ABSTRACT

Aim: The aim of the present study was to assess the ability of the biomarkers neuron-specific enolase (NSE) and S100 calcium-binding protein b (S100b) to predict mortality and poor neurologic outcome after 30 days in patients admitted with severe accidental hypothermia.

Methods: Consecutive patients with severe accidental hypothermia, defined as a core temperature $<32^{\circ}\text{C}$, were included. Patients were treated with active rewarming and/or extracorporeal life support (ECLS) using extra corporeal circulation (ECC) and/or extra corporeal membrane oxygenation (ECMO). The day following admission blood was analyzed for NSE and S100b. Follow-up was conducted after 30 days and poor neurologic outcome was defined as a Cerebral Performance Category (CPC) score of 3–5. The predictive value of NSE and S100b was assessed as the area under the receiver-operating characteristics curve (AUC).

Results: A total of 34 patients were admitted with a diagnosis of severe accidental hypothermia and 29 (85%) were resuscitated from cardiac arrest. ECLS was initiated in 27 (79%) of patients. The day following admission three (9%) patients had died and one (3%) patient was awake, and accordingly, NSE and S100b were analyzed in 30 unconscious and/or sedated patients. NSE and S100b achieved AUCs of 0.93 and 0.88, respectively, for prediction of 30 day mortality and AUCs of 0.88 and 0.87, respectively, for prediction of poor neurologic outcome.

Conclusions: In patients remaining unconscious the day following admission for severe accidental hypothermia, the biomarkers NSE and S100b appear to be solid predictors of mortality and poor neurologic outcome after 30 days.

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Introduction

In patients admitted to a hospital after suffering from accidental hypothermia (AH), defined as an involuntary drop in core temperature to below 35°C , in-hospital mortality is approximately 30% [1]. If severe AH is accompanied by associated cardiac arrest (CA), the

mortality has been reported as high as 90% [2,3], even after introduction of extra corporeal life support (ECLS) which is the treatment recommended by current guidelines [4].

AH is commonly classified according to a core temperature of $32\text{--}35^{\circ}\text{C}$ (Stage I), $28\text{--}<32^{\circ}\text{C}$ (Stage II), $<28^{\circ}\text{C}$ (Stage III), or absence of vital signs (Stage IV) [4,5]. Many victims in stage IV are already dead, and cannot be resuscitated and some patients may have severe neurologic injuries when admitted to hospital. The decision whether to resuscitate or not is difficult due to lack of reliable criteria of death, and during many years the only biochemical prognostic factor during AH has been hyperkalaemia [6]. Prognosis depends on a multitude of other factors including duration and severity of

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hypothermia, associated exposure such as hypoxia or trauma, individual patient characteristics such as age and comorbidities, time to treatment, prehospital management, etc. [7], and at present time the decision to withdraw care remains notoriously difficult.

In out-of-hospital cardiac arrest (OHCA), the biomarker neuron-specific enolase (NSE) has emerged as a marker of increased risk for poor neurologic outcome [8,9], and is suggested as part of a multimodal prognostication strategy by current guidelines [10,11]. The biomarker S100 calcium-binding protein b (S100b) has been suggested to be associated with poor outcome after diffuse axonal injury [12] and cardiac arrest [13], but is not a part of the current guidelines for prognostication after OHCA [10].

Considering the high mortality after severe AH and the resources involving treatment at highly specialized centres, a prognostic marker for outcome after AH would be of great benefit. This study aimed to assess potential prognostic markers of poor outcome in patients suffering from AH.

Methods

The present study is a prospective analysis of consecutive patients admitted to the intensive care unit (ICU) at our primary heart center with a diagnosis of AH with a core temperature $<32^{\circ}\text{C}$ (Stage II–IV⁵) from February 2011 to May 2017. Patients were admitted to a thoracic intensive care unit and actively rewarmed with surface rewarming and/or ECLS being initiated at the discretion of the treating intensive care consultant. For ECLS, extra corporeal circulation (ECC) or extra corporeal membrane circulation (ECMO) was applied at the discretion of the treating physician. On admission to the ICU, an arterial blood gas was drawn and analyzed. From one to three days after admission, blood was drawn daily and analyzed for NSE and S100b.

Analyses of NSE were performed with the Cobas 8000, e602 module, using an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics), with a range from 0.1 to 370 $\mu\text{g/L}$ and a between-run precision at 11 $\mu\text{g/L}$ and 85 $\mu\text{g/L}$ of 8% and 7%, respectively. Analyses of S100b were performed with the Cobas 8000, e602 module, using an ECLIA kit (Roche Diagnostics), with a range from 0.02 to 39 $\mu\text{g/L}$, and a between-run precision at 0.09 $\mu\text{g/L}$ and 3.3 $\mu\text{g/L}$ of 6%.

Follow-up was conducted by review of medical files, and one intensive care consultant adjudicated mortality and neurologic outcome 30 days after admission. Neurologic outcome was adjudicated and dichotomized according to the cerebral performance category (CPC) score. A poor neurologic outcome was defined as a CPC-score of 3–5 equivalent to severe disability, coma or death [14].

Extra corporeal life support

ECLS using cardiopulmonary bypass (CPB) or veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was performed in the presence of primary hypothermic cardiac arrest or severe circulatory instability refractory to advanced life support due to AH stage III–IV. The patients were cannulated primarily in the femoral artery, which often is the quickest and easiest way to establish emergency access. Sternotomy and cannulation of the right atrium and ascending aorta was performed in cases where cannulation of the femoral vessel was not feasible. CPR was continued until ECLS with rewarming had started. General anaesthesia was provided during the procedure and ventilation was gradually initiated as soon as ECLS had been established. ECLS-rewarming was started with circuit temperatures approximately the same as the admission temperature of the patient, avoiding large temperature gradients when ECLS commenced. Flows were increased gradually to 2.2–2.5 $\text{L min}^{-1}\text{m}^{-2}$ and a pressure >45 mmHg. We aimed

at a rewarming rate of 1°C per 10 min. ECLS was continued until the patient had a stable cardiac rhythm, adequate native perfusion and oxygenation, and a core temperature $>32^{\circ}\text{C}$. Inotropes or vasopressors were used as needed for weaning. Targeted temperature management was performed according to guidelines and post-resuscitation hyperthermia was avoided. Termination of ECLS was considered if there was no ROSC at 32–35 $^{\circ}\text{C}$. The decision to stop treatment was also based on additional clinical information.

Ethics

The Danish Patient Safety Authority (Institutional approval ref. 3-3013-1906/1) and the Danish Data Protection Agency approved study, and access to review patients' medical charts was granted. The study was conducted in accordance with Danish Legislation and the Helsinki Declaration.

Statistical analyses

Categorical variables were compared with the Chi-Square test or Fisher's Exact test as appropriate and presented as numbers (n) and percentages (%). Continuous variables were compared with the Student's *t*-test or the Mann-Whitney non-parametric test as appropriate, and presented as mean $\pm$ standard deviation (SD) if normally distributed or as median (inter-quartile range, IQR) if skewed.

To identify predictors of death, baseline characteristics were presented stratified by 30 day survival. In addition, we analyzed differences in arterial blood gas parameters on ICU admission stratified by 30 day survival. To assess the predictive value of NSE and S100b drawn the day following admission, we chose to conduct the remaining analyses on patients being unconscious/sedated and alive the day after admission. The reason for this was an expected low mortality in conscious patients, while including patients who died before first blood sample would introduce immortal time bias to the analyses.

We applied the area (AUC) under the receiver operating characteristics (ROC) curves to assess the predictive ability of the biomarkers for mortality and poor neurologic outcome after 30 days. These analyses were repeated on the subgroup with CA and the subgroup treated with ECLS.

In addition, for a false-positive rate (FRP) of zero, i.e. a specificity of 100%, we assessed the corresponding sensitivity for prediction of 30 day mortality. All tests were two-sided with a significance level of 0.05. All statistical analyses are done with SAS software 9.4.

Results

Pre hospital management

A total of 34 patients were admitted with an initial diagnosis of AH (Fig. 1). A total of 24 (71%) were male and median age was 33 years (IQR 20–56 years). The cause of AH was immersion/submersion in saltwater in 19 (56%) cases (Table 1). On emergency service (EMS) arrival 33 (97%) patients had a Glasgow Coma score (GCS) below 9. In addition, 23 (68%) patients were in clinical cardiac arrest with no spontaneous breathing and no palpable pulse. During EMS care a further three patients developed cardiac arrest and accordingly, 26 (76%) patients received cardiopulmonary resuscitation in the pre-hospital setting.

In hospital management

After admission to the emergency department (ED), a further three patients developed CA, and thus 29 (85%) patients experienced CA during AH. The median lowest recorded temperature was

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