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Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33°C and 36°C

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ABSTRACT

BACKGROUND Neuron-specific enolase (NSE) is a widely-used biomarker for prognostication of neurological outcome after cardiac arrest, but the relevance of recommended cutoff values has been questioned due to the lack of a standardized methodology and uncertainties over the influence of temperature management.

OBJECTIVES This study investigated the role of NSE as a prognostic marker of outcome after out-of-hospital cardiac arrest (OHCA) in a contemporary setting.

METHODS A total of 686 patients hospitalized after OHCA were randomized to targeted temperature management at either 33°C or 36°C. NSE levels were assessed in blood samples obtained 24, 48, and 72 h after return of spontaneous circulation. The primary outcome was neurological outcome at 6 months using the cerebral performance category score.

RESULTS NSE was a robust predictor of neurological outcome in a baseline variable-adjusted model, and target temperature did not significantly affect NSE values. Median NSE values were 18 ng/ml versus 35 ng/ml, 15 ng/ml versus 61 ng/ml, and 12 ng/ml versus 54 ng/ml for good versus poor outcome at 24, 48, and 72 h, respectively ($p < 0.001$). At 48 and 72 h, NSE predicted neurological outcome with areas under the receiver-operating curve of 0.85 and 0.86, respectively. High NSE cutoff values with false positive rates ≤5% and tight 95% confidence intervals were able to reliably predict outcome.

CONCLUSIONS High, serial NSE values are strong predictors of poor outcome after OHCA. Targeted temperature management at 33°C or 36°C does not significantly affect NSE levels. (Target Temperature Management After Cardiac Arrest [TTM]; NCT01020916) (J Am Coll Cardiol 2015;65:2104–14) © 2015 by the American College of Cardiology Foundation.

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Comatose patients admitted to an intensive care unit (ICU) after an out-of-hospital cardiac arrest (OHCA) have a mortality rate of around 50%. In the majority of cases, initial ICU mortality is driven by hemodynamic failure, whereas later morbidity and mortality are due to brain damage (1). A large proportion of patients die of withdrawal of life-sustaining therapies because of presumed poor prognosis (2,3). Thus, adequate prognostication tools for neurological outcome prediction are crucial for therapeutic guidance in this severely ill population.

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Biomarkers of brain damage, particularly neuron-specific enolase (NSE), have been widely studied as markers for outcome prognostication (4,5). The protein NSE is a 78kDa glycolytic enzyme involved in glucose metabolism and is mainly found in neuronal and neuroendocrine cells. Its half-life is approximately 24 h. Previous studies on patients not treated with hypothermia after cardiac arrest suggested a cutoff level of 33 ng/ml at 48 h to be predictive of death and poor neurological function (6); the American Academy of Neurology subsequently adopted this cutoff into prognostication guidelines (7). With the implementation of induced hypothermia and its assumed neuroprotective effect, the validity of this cutoff has been questioned. Subsequent studies yielded conflicting results, probably due to methodological issues and the lack of standardization of dosing methods (8). Consequently, current guidelines do not advocate NSE for outcome prediction (9), and a recent advisory statement suggests a cautious use of "high NSE levels" within a multimodal prognostication algorithm (10).

In this context of uncertainty, the TTM trial (Target Temperature Management After Out-of-Hospital Cardiac Arrest) (11), a multicenter clinical trial that included 950 patients randomized to targeted temperature management of 33°C or 36°C, provided a platform to investigate the role of NSE as a prognostic marker of outcome after OHCA in a contemporary setting.

ABBREVIATIONS AND ACRONYMS

CPC = cerebral performance category

FPR = false positive rate

ICU = intensive care unit

IDI = integrated discrimination improvement

NRI = net reclassification index

NSE = neuron-specific enolase

OHCA = out-of-hospital cardiac arrest

ROSC = return of spontaneous circulation

METHODS

All patients included in this study were part of the TTM trial (November 2010 to July 2013) comparing 2 temperature regimens in unconscious adult patients admitted to an ICU after an OHCA of a presumed cardiac cause. The TTM trial design, the statistical analysis plan, and the main results have been published previously (11–13). The randomization was stratified by site and performed centrally with adequate allocation concealment and sequence generation. A target temperature of 33°C or 36°C was initiated in each group according to allocation. At 28 h after start of the intervention, rewarming to 37°C was commenced at a maximum speed of 0.5°C/h. This pre-defined substudy of the TTM trial on NSE was approved by the steering committee before starting NSE analysis.

The TTM trial protocol was approved by ethical committees in each participating country, and informed consent was waived or obtained from all participants or relatives according to national legislations, in line with the Helsinki declaration (14).

Serum blood samples were taken from the patients at 24, 48, and 72 h after return of spontaneous circulation (ROSC). All samples were pre-analytically processed at the different sites, aliquoted, and frozen to −80°C before shipment to the Integrated BioBank of Luxembourg before analysis. NSE values were not available to the treating physicians during the trial.

NSE analyses were performed 6 months after trial completion at the clinical biology laboratory of the Centre Hospitalier de Luxembourg. All serum samples

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