RESEARCH LETTER

Impact of selected clinical factors on outcome of patients after out-of-hospital cardiac arrest treated with targeted temperature management

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Patients after out-of-hospital cardiac arrest (OHCA) and successful cardiopulmonary resuscitation (CPR) show various degrees of central nervous system damage. OHCA mainly occurs secondary to coronary artery disease or structural heart disease, but in some patients, the etiology remains unknown.[1] The prognosis following OHCA remains very poor, with only 4% of all OHCA patients surviving until hospital discharge.[2] The development of severe anoxic encephalopathy is responsible for more than 60% of deaths.[2] Targeted temperature management (TTM) is the only currently recommended method of neuroprotection in those patients.

Several recent studies clearly highlight the importance of prehospital treatment, including prompt initiation of effective CPR.[3] Despite a negative trend in survival seen for resuscitation times above 15 minutes, as in the study by Mooney et al,[3] nearly one-third of patients with OHCA to return of spontaneous circulation (ROSC) time greater than 30 minutes survived with cerebral performance category (CPC) scale 1–2.[3] Clearly, effective postresuscitation therapy, including a rapid correction of metabolic disturbances, active seizure control, and treatment of hyperglycemia, is an important prognostic factor. In multivariate analyses, the use of TTM was a major independent prognostic factor of good outcomes in several studies.[3]

Currently, we do not have adequate clinical evaluation tools that would allow prediction of short- and long-term treatment outcomes after OHCA. Our aim was to define the prognostic value of selected clinical and biochemical parameters in OHCA patients undergoing TTM. A dedicated scale could be used for stratification of patient outcome, careful patient selection, as well as optimal and rational health care resource distribution.

Our retrospective, single-center analysis included 50 consecutive adult OHCA patients admitted between 2012 and 2016 to the Coronary Care Unit of the 1st Department of Cardiology, Medical University of Warsaw (Poland), who were managed according to the TTM protocol that included set times for performing biochemical tests. All patients underwent neurological assessment by the same reviewer on admission and at discharge with the CPC scale (CPC 1, good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state; and CPC 5, brain death). The primary outcome was satisfactory neurological outcomes defined as CPC 1 and 2. Secondary outcome was all-cause in-hospital mortality. The TTM was performed using an external cooling device (Gaymar® Medi-therm III or Arctic Sun® Bard), with body temperature monitoring by esophageal temperature catheter. Patients were cooled to 33°C for 36 hours with a rewarming speed of 0.25°C per hour. If acute coronary syndrome was suspected as a cause of sudden cardiac arrest, patients underwent coronary angiography. All patients received similar pharmacological treatment, which included analgosedation (propofol/fentanyl) and 1 muscle relaxant (vecuronium bromide). Routinely, for the prevention of bacterial infection, broad-spectrum antibiotics were used. Other drugs were used according to the current guidelines.

Statistical calculations were performed using SAS 9.4. Quantitative variables were reported as median values and interquartile range. Categorical variables were presented as percentages. Nonparametric statistical tests were used due to nonnormally distributed variables. Risk factors for in-hospital mortality were determined using univariate logistic regression. A *P* value of 0.05 or less was considered significant.

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Received: September 6, 2018.
Revision accepted: December 17, 2018.
Published online: December 29, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2019; 129 (1): 61-64
doi:10.20452/pamw.4408

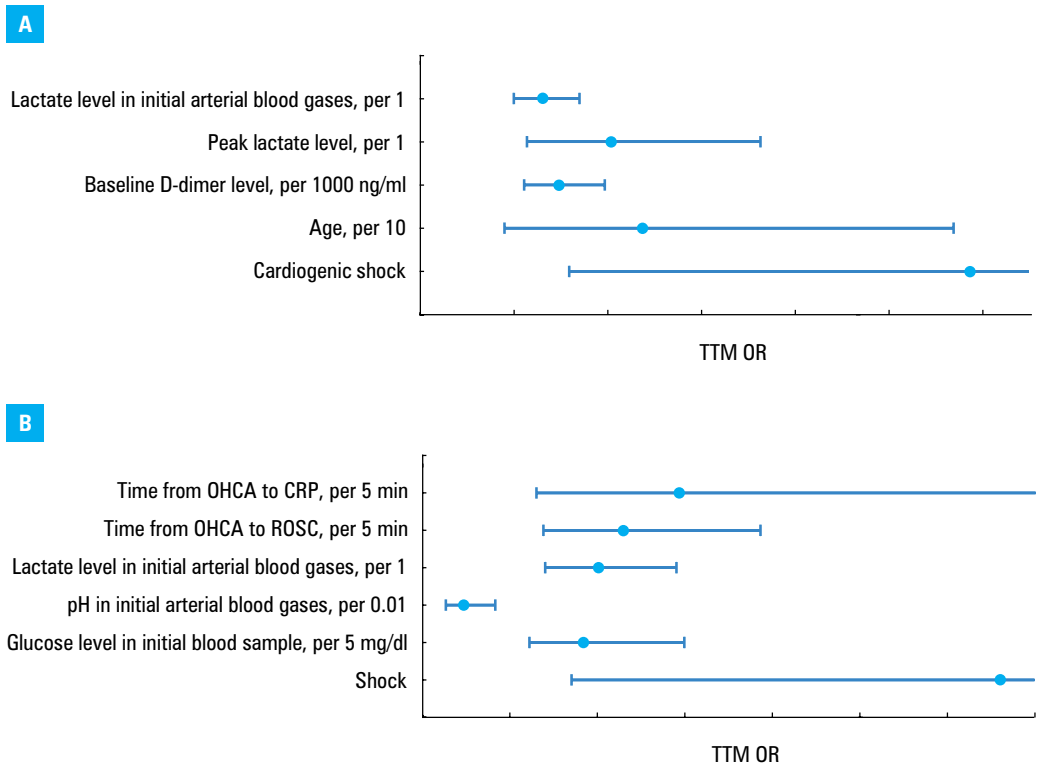

FIGURE 1 Effect of selected biochemical and clinical variables on all-cause mortality (**A**) and neurological status (**B**): results of a univariate analysis
Abbreviations: CRP, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; ROSC, return of spontaneous circulation; TTM, targeted temperature management

The study population included 50 patients, mostly men (n = 40; 80%) with a median age of 60 years (range, 52–66 years). ST-segment elevation myocardial infarction was diagnosed in 27 patients, and non–ST-segment elevation myocardial infarction, in 9. Emergency coronary angiography was performed in 31 patients, and percutaneous coronary intervention, in 29 cases. Clinical and biochemical characteristics were included in Supplementary material *Tables S1* and *S2*.

The median time from the OHCA to the CPR was 5 minutes (range, 1–10 min), and the time from the OHCA to the ROSC, 20 minutes (range, 5–30 min). The median time from the OHCA to the initiation of TTM was 120 minutes (range, 60–210 min), and the time from the ROSC to the target temperature during TTM, 360 minutes (range, 240–458 min). The mean time of rewarming to 36.6°C after hypothermia was 720 minutes (range, 488–1295 min). In most cases, the OHCA mechanism was ventricular tachycardia (VT) or ventricular fibrillation (VF) (82%). Asystole occurred in 18% of cases. Pulseless electrical activity was not registered in any patient.

In-hospital mortality was 40.0%. In univariate logistic regression, an increased mortality risk was associated with the following variables: baseline lactate level (per 1) (odds ratio [OR], 1.31; 95% CI, 1.00–1.70; $P = 0.049$), peak lactate level (per 1) (OR, 2.04; 95% CI, 1.14–3.63; $P = 0.016$), and minimal pH value (per 0.01) (OR, 0.66; 95% CI, 0.47–0.94; $P = 0.02$). The D-dimer level was also associated with patient survival in this group (baseline D-dimer level [per 100 ng/ml]: OR, 1.04; 95% CI, 1.01–1.07; $P = 0.01$). Patient age was not associated with an increased mortality risk (OR, 1.09; 95% CI, 0.99–1.19; $P = 0.07$). Development of shock, diagnosed in 34% of patients, was associated with approximately 6-fold increased mortality (OR, 5.87; 95% CI, 1.59–21.6; $P = 0.01$).

The neurological status of patients at baseline was CPC 4, Glasgow Coma Scale 4. Following treatment, a good neurological status was observed in 26 patients (52%). After exclusion of patients with shock, the CPC score 1–2 was observed in a higher proportion of patients (65%).

Final neurological outcomes of the treatment were associated with some CPR procedure details and biochemical parameters. In a univariate logistic regression, a difference was found between the time from OHCA to CPR (OR, 1.24; 95% CI, 1.05–1.45; $P = 0.009$) as well as OHCA to ROSC (OR, 1.18; 95% CI, 1.07–1.31; $P = 0.001$) and the final CPC score. The final neurological outcome was associated with the baseline lactate concentration (OR, 1.151; 95% CI, 1.07–1.24; $P = 0.007$) and baseline arterial pH (OR, 0.47; 95% CI, 0.27–0.84; $P = 0.007$). The highest blood glucose concentration during treatment also influenced the final neurological outcome (OR, 1.13; 95% CI, 1.04–1.25; $P = 0.005$). We did not find any correlation between the neurological outcome and OHCA to TTM (33°C) time nor glomerular filtration rate, creatinine, troponin, C-reactive protein, and D-dimer concentrations.

Our results show that the final neurological outcome was related to many independent parameters, most importantly, times from the OHCA to CPR, ROSC, and initiation of TTM. However, we did not find a correlation between the neurological outcome and the time from the OHCA to reach the target cooling temperature. We suspect that quick body temperature control and fever prevention in OHCA survivors

but not achieving the target temperature of 33°C is protective. This corresponds to the findings of Nielsen et al,[4] where no additional benefit from a target temperature of 33°C compared with 36°C was found.

Our findings reveal several parameters that are potentially clinically useful, including biochemical tests, which strongly correlate with the final neurological outcome. The most important adverse prognostic factors included the lactate level, pH in initial arterial blood gases, and the peak lactate level during intensive therapy.

An increased lactate level persisting despite optimal therapy may be considered as a marker of postresuscitation organ damage degree and a marker of impending multiorgan failure. In other studies, a higher lactate concentration was associated with increased 30-day mortality and worse neurological outcomes at 3 months.

Another important prognostic parameter was the D-dimer level on admission. An elevated D-dimer concentration is typical of patients after successful CPR, reflecting profound activation of thrombosis and endogenous fibrinolysis secondary to metabolic shock due to tissue hypoxia.[5]

In our population, 6 of 50 patients developed acute kidney injury (AKI) during hospitalization. Although some studies have shown that kidney function is associated with worse survival after OHCA and TTM,[6] this was not observed in our study. Importantly, the TTM procedure has no significant effect on renal function compared with the normothermia group as shown in a meta-analysis of randomized controlled trials.[7]

Another interesting association was found between adverse neurological outcomes and hyperglycemia persisting despite treatment. Hyperglycemia after OHCA has a negative impact on survival and neurological outcomes.[8] One of the possible mechanisms is modulation of neuronal homeostatis. Hyperglycemia is linked with a rise in neuronal apoptosis, increased microglial and astrocytes activation, as well as an increase in the hippocampus and frontal cortex neuron damage.[9]

The presence of shock on admission was the strongest risk factor for negative outcome, which was associated with a nearly 6-fold increase in the risk of death. Despite significantly increased mortality among patients with shock, the neurological condition of survivors was similar to that of patients without shock.[10] Similar observations were made in the COOL IT study. Mooney et al[3] found no significant association between the age of patients subjected to TTM and in-hospital mortality. However, a significant effect on the final neurological outcome was reported. In the present study, we observed no impact of age on mortality or neurological outcome.

Small patient samples in the present study did not allow a separate analysis of the impact of initial rhythm of the patient on examined parameters. Nonetheless, it deserves a comment, as it is widely discussed in literature. Available data indicate better outcomes in patients with OHCA and TTM only in patients with shockable rhythms.[11] In contrast to VT/VF, asystole and pulseless electrical activity are associated with poor prognosis even when TTM is used, although one study showed some reduction of in-hospital mortality with TTM usage compared with normothermia (OR, 0.84; 95% CI, 0.78–0.92).[12]

Several biochemical factors measured on admission, clinical state, the time from OHCA to CPR, and the time from OHCA to ROSC can affect outcomes at discharge in patients treated with TTM. Cardiogenic shock on admission is a strong predictor of negative neurological outcome and all-cause mortality. The development of an appropriate prognostic score would be useful to identify those patients who will benefit the most from neuroprotective treatment. Parameters described in our study should be prospectively evaluated.

SUPPLEMENTARY MATERIAL Supplementary material is available with the main article at www.pamw.pl.

ACKNOWLEDGMENTS This project, as part of Polish Registry for Therapeutic Hypothermia (PRTH), was supported by the CR BARD.

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