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SHORT COMMUNICATION

Efficacy and safety of prolonged mild therapeutic hypothermia treatment in patients after out-of-hospital cardiac arrest: preliminary data

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INTRODUCTION

The only proven method of neuroprotection in patients after out-of-hospital cardiac arrest (OHCA) is target temperature management (TTM). Results of a recent survey study showed that the prevalence of TTM in Poland is still low. Only about one-third of the intensive care units that responded to the survey use such a method [1].

According to the current European Resuscitation Council (ERC) 2015 Guidelines, a constant temperature of between 32°C and 36°C should be maintained for at least 24 h; however, the optimal duration of TTM remains unclear [2]. When we started conducting the study, ERC 2010 Guidelines recommended maintaining a temperature of between 32°C and 34°C [3]. Thus, the term mild therapeutic hypothermia (MTH) will be used instead of the now preferred TTM or temperature control [2]. The efficacy, safety, and risk factors for unfavourable neurological outcomes of prolonged external MTH in OHCA patients are presented.

METHODS

It was a retrospective single-centre study that included 65 adult survivors of OHCAs due to cardiac pathologies. Patients after OHCA secondary to poisoning, trauma, or respiratory failure were excluded.

A comparison was made between 28 consecutive patients hospitalised between 2011 and 2013 in the coronary care unit (CCU) of the 1st Chair and Department of Cardiology treated with MTH and a historical control group of 37 consecutive patients admitted to the CCU between 2009 and 2011. Patients from the control group were not subjected to MTH because it was not used at our hospital at that time.

Efficacy was measured by neurological outcomes (Glasgow Coma Scale [GCS] and Cerebral Performance Category [CPC] evaluated on admission and at discharge) and in-hospital mortality. Scores from one to two points in CPC and from 13 to 15 points in GCS were considered as a good neurological outcome.

Initial cooling was started in the catheterisation lab (fast 4°C saline solution infusion or external cooling blankets). Core temperature was measured by a temperature catheter placed in the oesophagus. Subsequently, stationary cooling with external blankets with established core temperature of 33°C was maintained for 36 h. During rewarming a temperature was increased by 0.25°C/h. After their temperature reached 36.6°C, patients were monitored by the device in standby mode for 8 h to 12 h to prevent hyperthermia. According to the MTH protocol, to achieve level 4 or 5 on the Ramsey Scale patients received a combination of opiates and propofol or midazolam. To obtain muscle relaxation rocuronium was used.

Statistical analysis was performed using statistical packages Statistica (StatSoft Polska, Kraków, Poland) and SPSS 21 (IBM Corporation, Armonk, NY, USA). Quantitative variables were presented as medians and interquartile ranges. Due to the non-normal distribution of variables, nonparametric tests were used: the Kruskal-Wallis analysis of variance with post-hoc test and the Mann-Whitney U test for comparison between groups. For categorical data the χ^2 test was used. Risk factors for in-hospital death were investigated in univariate logistic regression analysis. A level of statistical significance was assumed at $p \leq 0.05$.

RESULTS AND DISSCUSSION

Both groups were similar with regard to the demographic parameters, concomitant diseases, cardiovascular risk factors, and initial admission diagnosis (**Supplementary Table 1**

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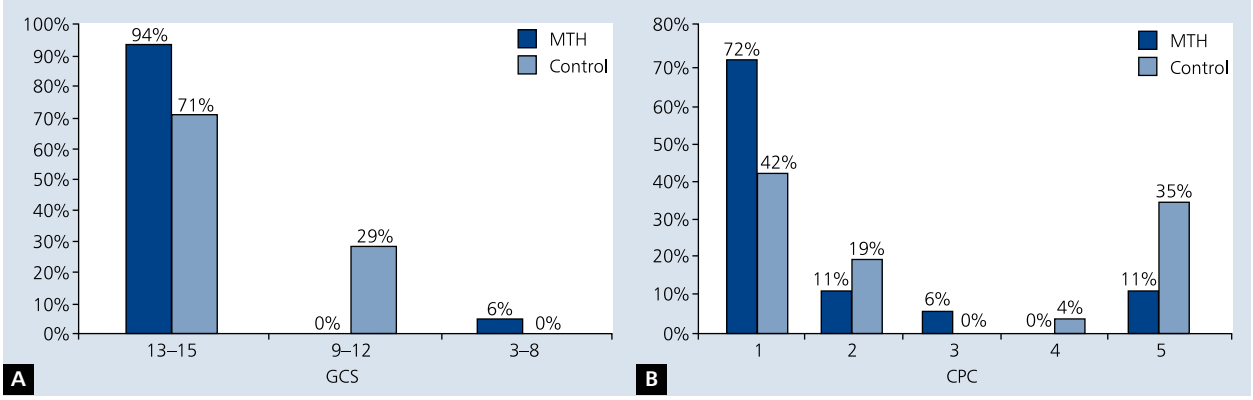

Figure 1. The percentage distribution of neurological outcomes after treatment in Glasgow Coma Scale (GCS) (**A**) and Cerebral Performance Category (CPC) (**B**) in patients treated with mild therapeutic hypothermia (MTH) and the control group, with exclusion of patients with cardiogenic shock

— see journal website). ST-segment elevation myocardial infarction was the final diagnosis in 15 (53.6%) patients from the MTH group vs. 13 (35.1%) patients from the control group (p = 0.137), and non ST-segment elevation myocardial infarction in four (14.3%) patients from the MTH group vs. 14 (37.8%) patients from the control (p = 0.036). In both the MTH group and the control 15 patients had percutaneous coronary intervention (53.6% vs. 40.5%; p = 0.297). The median temperature during the procedure was 33.2°C (33.0–33.6°C). The median rewarming time to 36.6°C was 720 min (488–1295 min).

There were no differences between neurological state at admission (CPC 4 points in both groups, the median score in GCS 4 [3–5] points in the MTH group vs. 3 [3–5] points in the control group; p = 0.075) or after treatment (CPC and GCS: p = 0.09, p = 0.16, respectively) between the studied groups (**Supplementary Figure 1 — see journal website**). However, after excluding patients with cardiogenic shock from the analysis (MTH group — five patients, control group — seven patients), the benefits of the hypothermia were more pronounced: the MTH group had better neurological outcomes assessed in GCS (p = 0.016) and CPC (p = 0.018) (Fig. 1). In the HACA randomised trial good neurological outcomes in CPC were achieved by 39% of patients from the control and 55% from the MTH group (p = 0.009) [4]. In a retrospective meta-analysis Arrich et al. [5] observed satisfactory outcome in CPC in 63.1% of patients from the MTH group and 32.5% from the control group. It should be remembered that cardiogenic shock was one of the most important exclusion criteria in the qualification protocols in the first MTH studies influencing the comparison of our results with other studies [4, 6].

In the univariate logistic regression cardiogenic shock significantly increased the risk of unfavourable neurological outcomes (CPC 3–5 points, odds ratio [OR] 6.6, 95% confidence interval [CI] 1.7–25.6; p = 0.006) and in-hospital mortality (OR 5.7, 95% CI 1.59–21.6; p = 0.008).

Biochemical predictors of in-hospital mortality in the MTH group assessed by the univariate analysis comprised lactic acid concentration on admission (OR 1.45, 95% CI 1.072–1.978; p = 0.01), lactic acid concentration (OR 1.85, 95% CI 1.074–3.212; p = 0.02), and blood pH (OR 0.001, 95% CI 0.001–0.008; p = 0.01) in the most abnormal arterial blood gas analysis. The prognostic value of baseline lactic acid level measured in the first conducted arterial blood gas analysis has previously been observed [7, 8], as was the association between lower baseline lactic acid concentration and better neurological status in GCS three months after MTH treatment [8]. Moreover, increased D-dimer concentration on admission (OR 1.36, 95% CI 1.040–1.773; p = 0.02) and at the end of the therapy (OR 2.3, 95% CI 1.170–4.667; p = 0.01) turned out to be an important mortality predictor.

In the control group the risk factors for in-hospital mortality were: blood pH in arterial blood gas analysis on admission (OR 0.38, 95% CI 0.174–0.821; p = 0.01) and lactic acid concentration on admission (OR 1.4, 95% CI 1.11–1.78; p = 0.004). Additional risk factors for this group included initial diastole blood pressure (OR 0.96, 95% CI 0.927–1.000; p = 0.04), initial value in GCS (OR 0.23, 95% CI 0.08–0.64; p = 0.01), time since OHCA to the beginning of cardiopulmonary resuscitation (OR 1.2, 95% CI 1.005–1.44; p = 0.04), time since OHCA to the return of spontaneous circulation (OR 1.12, 95% CI 1.023–1.225; p = 0.01), and the last obtained creatinine level (OR 3.11, 95% CI 1.18–8.19; p = 0.02).

A separate comparison of complications was performed. No significant differences regarding in-hospital mortality were observed: 10 (35.7%) patients from the MTH group vs. 15 (40.4%) patients from the control (p = 0.692) died (**Supplementary Table 2 — see journal website**). Occurrence of a ventricular tachycardia/ventricular fibrillation,

pulseless electrical activity, paroxysmal atrial fibrillation, sepsis, pneumonia, haemorrhage, or acute kidney injury was similar in both groups (**Supplementary Table 3 — see journal website**). The percentage of complications in our study was comparable to the values reported in other research [4, 9]. Interestingly, asystole occurred more frequently in the control group (two [7.1%] patients vs. ten [27%] patients; p = 0.04). The physiological explanation remains unclear. It is known that hypothermia results in bradycardia and prolonged PR, QRS, and QT intervals [10].

The area under the receiver operating characteristic curve for the occurrence of complications was the largest for age (value 0.79), shock (0.67), and heart failure (0.66) (**Supplementary Figure 2 — see journal website**).

The main limitation of the study is its retrospective design and lack of randomisation. Second, the studied groups were small, so multivariable analysis was not performed.

Conflict of interest: *none declared*

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