Journal Club

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Pfeifer R, Franz M, Figulla HR. Hypothermia after cardiac arrest does not affect serum levels of neuron-specific enolase and protein S-100b. Acta Anaesthesiol Scand 2014;58:1093-100.

Therapeutic hypothermia (TH) is a treatment option in comatose survivors of out-of-hospital cardiac arrest (CA) after ventricular fibrillation.[1] The patients are mechanically ventilated and receive sedative drugs for several days making clinical neurological examination difficult. The predictors of neurological outcome such as brain-derived proteins neuron-specific enolase (NSE) and protein S-100b are needed. They are widely used as prognostic markers for evaluating the severity of hypoxic brain injury in comatose survivors of CA.[2]

The present study included 201 comatose adult patients who had suffered in or out of hospital nontraumatic CA. They were admitted to intensive care unit (ICU) between January 2003 and June 2010. The patients who reacted adequately during 1 h observation phase without sedation and those who died during the first 48 h after CA were excluded from the study. TH was applied to 140 patients (30 female, 110 male, mean age −63.2 ± 14.4 years), whereas 61 (24 female, 37 male, mean age −67.8 ± 14.2 years) received comparable intensive care therapy without hypothermia. TH was applied according to criteria published by authors in resuscitation,[3] but later adapted according to the recommendation of European Resuscitation Council.[1,4] Serum levels of NSE and S-100b were assessed first immediately on ICU admission and then subsequently until 5 days after restoration of spontaneous circulation (ROSC) using commercial immunoluminometric assay with a LIAISON analyzer. The reference values were 12.5 ng/ml for NSE and 0.15 mcg/L for S-100b. The levels did not influence therapeutic decisions during the first 7 days after ROSC.

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Therapeutic hypothermia was applied either by surface cooling or intravascular cooling to maintain body core temperature (measured with a bladder temperature probe) within a narrow range 33 ± 0.5°C for 24 h. Rewarming was achieved passively in surface cooled patients and actively (0.3°C/h) in intravascular cooled patients. After 4 weeks, the patients were classified according to Pittsburgh Cerebral Performance Category Scale (CPC).[5] The patents were divided into two groups; those with poor outcome, that is, those who died or remained comatose (CPC 4 and 5) and those who had good to moderate neurological recovery that is, recovery of at least cognitive brain function and survival with neurological disabilities of variable severity or without any neurological impairment (CPC 3-1).

In the hypothermia group (HG), 61 of 140 patients (43.6%) and in the normothermia group (NG) 26 of 61 patients (42.6%) survived the first 4 weeks after ROSC with moderate to good neurological outcome. Due to adhering to the guidelines for TH, HG patients were significantly younger than NG patients (P = 0.012), and CA occurred more frequently in out-of-hospital area. The mean application time of hypothermia amounted to 23.9 h and the target body core temperature (32.5–33.5°C) was maintained for 16.9 h. The duration of re-warming to a core temperature of 36°C averaged 9.1 h. A significantly higher level of NSE and S-100b were observed on day 4 and 5 respectively in HG when compared to NG. By trend, the serum levels of both proteins were lower in the NG.

An intra-aortic balloon pump had to be applied to 38 (27%) of HG and 11 (18%) of NG patients. For NG and HG patients with unfavorable neurological outcome (CPC 4 and 5), on each day significantly higher NSE and S-100b were found when compared with those with CPC 3-1. Taking groups together, 87 patients survived with CPC 3-1; in several patients NSE levels exceeded the threshold of 33 ng/ml. On the 3rd day, NSE levels ≥40 ng/ml predicted poor neurological outcome with a sensitivity 74.1% (confidence interval [CI] = 0.6475–0.8203), a specificity 95.2% (CI = 0.8825–0.9869), a positive predictive value (PPV) of 95.2% (CI = 0.8825–0.9869).

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Whereas, S-100b levels ≥1.03 mcg/L on the 3rd day had sensitivity 57.8% (CI = 0.4544–0.6939), specificity 95.6% (CI = 0.8782–0.9909), PPV 93.2% (CI = 0.8134–9857) for poor neurological outcome.

The improved survival rate in HG patients was not observed, which was also the case in the previous trial published in 2013.[6] There was a tendency for the serum levels of both proteins to be higher in HG patients. Lower NSE levels have been reported earlier in HG patients but in those studies more patients had favorable neurological outcome.[7] The authors consider it unlikely that the kinetics of the two proteins were changed by TH. There is increasing evidence that resuscitated patients with NSE concentration much higher than the cut-off level can survive with moderate or good neurological outcome. Hemolysis or several forms of cancer may influence levels of NSE; similarly, S-100b is released from tissues other than brains such as adipocytes, chondrocytes and several forms of cancer of central nervous system and melanoma.

The authors conclude that TH has no influence on NSE and S-100b serum levels in comatose CA survivors. The increase in both the proteins indicate poor neurological outcome; hence, their measurement is an additional tool for making prognosis on comatose CA survivors. However, at present it is not possible to recommend reliable threshold protein concentration, further investigations in this field are warranted.

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Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, *et al.* A Comparison of Propofol- and Dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014;121:978-89.

Electroencephalogram pattern observed during sedation with dexmedetomidine appear similar to those observed during general anaesthesia with propofol. However, these drugs have different molecular mechanisms and behavioural properties and are likely accompanied by different neural circuit dynamics. Whether the differing clinical effects of these drugs can be distinguished by their electroencephalogram signature is unclear.

The authors hypothesized that propofol-induced slow oscillations would have lower coherence and larger power/amplitude than dexmedetomidine induced slow oscillations. Sleep-spindles observed during sleep and dexmedetomidine induced unconsciousness have morphology that is intermittent in nature in contrast to propofol-induced frontal alpha oscillations which are continuous in nature. They further hypothesized that alpha-oscillations induced during general anaesthesia with propofol are different and significantly more coherent than the dex-spindle induced during sedation with dexmedetomidine.

The authors measured 64-channel electroencephalogram under dexmedetomidine (n = 9) and propofol (n = 8) in healthy volunteers, 18–36 years of age. In addition to standard preanesthesia assessment, a urine toxicology screen and urine pregnancy test for each female was performed. After adequate fasting of 8 h, the subjects were administered dexmedetomidine loading bolus 1 mcg/kg over 10 min followed by 0.7 mcg/kg/h (50 min) in dexmed-group. For propofol, the authors used a computer controlled infusion to target the effect site concentration of 0–5 mcg/ml and each concentration level was maintained for 14 min. The subjects were administered oxygen and respiration was assisted with bag-mask ventilation if apnea occurred. The monitoring included heart rate, electrocardiogram, oxygen saturation, respiration and expired carbon dioxide with capnography and blood pressure cuff (dexmedetomidine) or arterial line (propofol). Electroencephalography (EEG) was recorded using 64-channel Brain Vision Magnetic Resonance Imaging Plus System (Brain Products Munich, Germany) with a sampling rate of 1000 Hz (dexmedetomidine) and 5000 Hz (propofol), resolution 0.5 μV least significant bit and bandwidth 0.016–1000 Hz. Volunteers were instructed to close their eyes; and asked to respond by button presses when auditory stimuli were given to assess the level of consciousness.