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Clinical paper

Prolonged targeted temperature management compromises thrombin generation: A randomised clinical trial☆

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ABSTRACT

Aim: To investigate whether prolonged compared with standard duration of targeted temperature management (TTM) compromises coagulation.
Methods: Comatose survivors after out-of-hospital cardiac arrest (n = 82) were randomised to standard (24 h) or prolonged (48 h) duration of TTM at 33 ± 1 °C. Blood samples were drawn 22, 46 and 70 h after attaining the target temperature. Samples were analysed for rotational thromboelastometry (ROTEM® (EXTEM®, INTEM®, FIBTEM® and HEPTEM®)) and thrombin generation using the Calibrated Automated Thrombogram® assay.
Results: With the 22-h sample, we revealed no difference between groups in the ROTEM® and thrombin generation results beside a slightly higher EXTEM® and INTEM® maximum velocity in the prolonged group (p-values ≤0.04). With the 46-h sample, ROTEM® showed no differences when using EXTEM®; however, 11% (p < 0.01) longer clotting time and 12% (p < 0.01) longer time to maximum velocity were evident in the prolonged group than in the standard group when using INTEM®. The prolonged group had reduced thrombin generation compared with the standard group as indicated by 30% longer lag time (p = 0.04), 106 nM decreased peak concentration (p < 0.001), 36% longer time to peak (p = 0.01) and 411 nM*minute decreased endogenous thrombin potential (p < 0.001). With the 70-h sample, no differences in ROTEM® results were found between groups. However, the prolonged group had reduced thrombin generation indicated by longer lag time, decreased peak concentration and longer time to peak (all p-values ≤ 0.02) compared with the standard group.
Conclusion: Prolonged TTM in post-cardiac arrest patients impairs thrombin generation.
ClinicalTrials.gov identifier: NCT02258360.

Background

Few patients are resuscitated from a sudden cardiac arrest outside hospital [1]; these few are at major risk of subsequent brain damage and death [2]. To prevent severe brain damage, the International Liaison Committee on Resuscitation (ILCOR) recommends treating comatose out-of-hospital cardiac arrest survivors with targeted temperature management (TTM) [3]. However, the exact target temperature and the duration of TTM remain ongoing issues.

Hypothermia *per se* impairs haemostasis in trauma and surgery patients, which increases the risk of bleeding [4,5]. Thus, cardiac arrest patients with an impending risk of bleeding are considered to have a relative contraindication to treatment with TTM [6].

Previous studies have investigated the effect of standard TTM on haemostasis; however, to our knowledge, only one non-randomised, retrospective cohort study has investigated the effect of prolonged TTM [7].

Thromboelastometry (ROTEM®/TEG®) describes both clot initiation, clot development and clot firmness [8] and is increasingly

Abbreviations: APTT, activated partial thromboplastin time; C, Celcius; CI, confidence intervals; ETP, endogenous thrombin potential; ICU, Intensive Care Unit; INR, international normalised ratio; IQR, inter quartile range; ROSC, return of spontaneous circulation; SAPSII, Simplified Acute Physiology Score II.

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used in bleeding patients. Calibrated automated thrombin generation is a well-defined method used to describe the dynamics of thrombin generation [9].

The aim of the present study was to clarify whether treatment with prolonged TTM at 33 °Celcius (C) after out-of-hospital cardiac arrest induced a significant change in coagulation compared with standard duration of TTM. We hypothesised that prolonged duration of TTM impaired coagulation compared with standard duration of TTM.

Methods

We investigated comatose survivors after out-of-hospital cardiac arrest randomised to either 24 h (standard group) or 48 h (prolonged group) of TTM at 33 ± 1 °C (Fig. 1). The present study is an independent sub-study of the trial entitled "Time differentiated therapeutic hypothermia" (ClinicalTrial.gov identifier: NCT01689077) [10]. Patients were included within the time interval of February 2013 through May 2015 at the Intensive Care Unit, Aarhus University Hospital, Denmark. The inclusion criteria were as follows: obtained return of spontaneous circulation (ROSC) after cardiac arrest outside hospital with a presumed cardiac origin, Glasgow Coma Scale Score below 8, and age 18 years to 80 years. The exclusion criteria were the following: more than 60 min from circulatory collapse to ROSC, severe persistent cardiogenic shock despite use of vasopressor, more than 4 h from cardiac arrest to initiation of TTM, a cerebral performance category of 3–4 before the cardiac arrest, intracerebral haemorrhage or a pre-existing coagulopathy (not medically induced) [10]. Written informed consent was obtained from the next of kin and the general practitioner, and subsequently from the patients themselves if they became capable of giving informed consent. The study was approved by the Danish Data Protection Agency (number 1–16-02-284-13) and the Central Denmark Region Committees on Health Research Ethics (journal no. 20110022). Of the 82 patients included in the present study, 40 patients have previously been described by Jeppesen et al. [11,12] The manuscript follows the CONSORT statement.

To initiate cooling shortly after the cardiac arrest, all patients were protocolised to receive 30 ml/kg 4 °C isotonic saline either at the pre-hospital setting or upon admission. Cooling was continued either by intravascular cooling (ICY® catheter, Thermogard XP, Zoll, US) or surface cooling (Allon CureWrap®, CritiCool, MTRE, Israel). The patients were subsequently rewarmed at a rate of 0.5 °C/hour until normothermia (37 °C) was reached. The core temperature was continuously monitored by a thermo catheter (Coviden™, Ireland) at the intensive care unit and by rectal temperature measurements in the ward. During the intensive care unit stay, crystalloids and diuretics were administered intravenously to maintain urinary output above 1 ml/kg/hour, and patients were sedated with propofol and remifentanil/fentanyl.

Blood samples

An initial blood sample was obtained upon hospital admission (admission sample). Ensuing blood samples were collected 22 ± 2 h (22-h sample), 46 ± 2 h (46-h sample) and 70 ± 2 h (70-h sample) after the target temperature was reached (Fig. 1). Blood samples were drawn from an arterial line or, if infeasible, from a central venous catheter or the cubital vein using a 21G needle.

All blood samples were analysed for the following: blood cell count using an XE-5000 haematology analyser (Sysmex, Kobe, Japan), international normalised ratio (INR), activated partial thromboplastin time (APTT), thrombin time, antithrombin and functional fibrinogen using CS2100i (Sysmex, Kobe, Japan), blood lactate employing ABL800 FLEX (Radiometer, Brønshøj, Denmark) and C-reactive protein (CRP) using Cobas 6000 (Roche, Mannheim, Germany). At the 22-h sample, the 46-h sample and the 70-h sample, citrate anticoagulating tubes were used for rotational thromboelastometry (ROTEM® (Tem International GmbH, Munich, Germany)) and thrombin generation analyses. Tubes for ROTEM® analyses were kept at the preheating station at 37 °C for 30 min before initiating analyses with the assays EXTEM®, INTEM®, FIBTEM® and HEPTEM® (Tem International GmbH, Munich, Germany). From the ROTEM® results, clotting time, maximum velocity, time to maximum velocity and maximum clot firmness were used for further analysis. Citrate blood (Terumo Europe, Leuven, Belgium) for the thrombin generation analyses was centrifuged at 20 °C for 25 min. Then, plasma was separated and stored at −80 °C. When performing thrombin generation analyses, the plasma samples were thawed and each sample was analysed according to the manufacturer's instructions at 37 °C using the Calibrated Automated Thrombogram® Assay with the latest software update (Stago, Asniéres sur Seine, France). The plasma had not been thawed before analyses, and all samples were analysed using the same batch.

The Thrombinoscope® software calculated lag time, peak height, time to peak and endogenous thrombin potential (ETP).

Clinical information was systematically collected from electronic medical records and managed using REDCap (Research Electronic Data Capture) [13]. After the first day at the intensive care unit, the Simplified Acute Physiology Score II (SAPS II) [14] was calculated. Data regarding the cardiac arrest were collected according to the Utstein guidelines [15].

Statistics

Basing our sample size calculation on results from the first 40 patients included [11], we found a mean ROTEM® EXTEM® clotting time of 63 s and a standard deviation of 16 s. With a minimally relevant difference of 20% between the two intervention groups (12 s), a power of 90% and a two-sided significance level of 5%, we needed to include 39 patients in each intervention group.

Normality was checked using Q–Q plots. Data are presented as numbers (percentages) or as medians (25th percentiles – 75th percentiles (IQR)). To test for baseline differences between groups, a Wilcoxon Mann-Whitney *U* test was used for continuous variables and a Fisher's exact test was used for dichotomous variables. The ROTEM® and thrombin generation analyses were analysed using a multivariate repeated measurements ANOVA. The assumption of the model was checked by testing for equal standard deviations and correlations between groups, by checking that the residuals did not deviate from normality and by graphing the standardised residuals against the fitted values. Data were log-transformed if a better model fit could be obtained. The statistical analyses and graphics were performed using STATA® version 13 (StataCorp LP, College Station TX, USA).

Results

Fig. 1 illustrates that of 210 patients assessed for eligibility, 82 were included in the present study and thereby in the analyses; 42 were randomised to standard and 40 to prolonged duration of TTM. Of the patients included, four died within the study period; one patient from each group prior to the 46-h sample, and two patients in the standard group prior to the 70-h sample. Additionally, four samples were missing due to transfer or logistical difficulties: two in the 46-h sample and two in the 70-h sample.

Most patients were male (87%) and the median age was 60 years (range: 18–79 years). For baseline characteristics, see Table 1. After the cardiac arrest, the majority used aspirin, and approximately