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Nutma, Sjoukje; Tjepkema-Cloostermans, Marleen C; Ruijter, Barry J; Tromp, Selma C; van den Bergh, Walter M; Foudraine, Norbert A; H M Kornips, Francois; Drost, Gea; Scholten, Erik; Strang, Aart

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Effects of targeted temperature management at 33 °C vs. 36 °C on comatose patients after cardiac arrest stratified by the severity of encephalopathy


Departments of Neurology and Clinical Neurophysiology, Medical Spectrum Twente, Enschede, the Netherlands

Department of Clinical Neurophysiology, Technical Medical Center, University of Twente, Enschede, the Netherlands

Departments of Neurology and Clinical Neurophysiology, St Antonius Hospital, Nieuwegein, the Netherlands

Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Department of Intensive Care, VieCuri Medical Center, Venlo, the Netherlands

Department of Neurology, VieCuri Medical Center, Venlo, the Netherlands

Departments of Neurology and Neurosurgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Department of Intensive Care, St Antonius Hospital, Nieuwegein, the Netherlands

Department of Intensive Care, Rijnstate Hospital, Arnhem, the Netherlands

Department of Neurology, Medical Spectrum Twente, Enschede, the Netherlands

Abstract

Objectives: To assess neurological outcome after targeted temperature management (TTM) at 33 °C vs. 36 °C, stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h.

Design: Post hoc analysis of prospective cohort study.

Setting: Five Dutch Intensive Care units.

Patients: 479 adult comatose post-cardiac arrest patients.

Interventions: TTM at 33 °C (n = 270) or 36 °C (n = 209) and continuous EEG monitoring.

Measurements and main results: Outcome according to the cerebral performance category (CPC) score at 6 months post-cardiac arrest was similar after 33 °C and 36 °C. However, when stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h after cardiac arrest, the proportion of good outcome (CPC 1–2) in patients with moderate encephalopathy was significantly larger after TTM at 33 °C (66% vs. 45%; Odds Ratios 2.38, 95% CI = 1.32–4.30; p = 0.004). In contrast, with mild encephalopathy, there was no statistically significant difference in the proportion of patients with good outcome between 33 °C and 36 °C (88% vs. 81%; OR 1.68, 95% CI = 0.65–4.38; p = 0.282). Ordinal regression analysis showed a shift towards higher CPC scores when treated with TTM 33 °C as compared with 36 °C in moderate encephalopathy (cOR 2.39; 95% CI = 1.40–4.08; p = 0.001), but not in mild encephalopathy (cOR 0.81 95% CI = 0.41–1.59; p = 0.537). Adjustment for initial cardiac rhythm and cause of arrest did not change this relationship.

Conclusions: Effects of TTM probably depend on the severity of encephalopathy in comatose patients after cardiac arrest. These results support inclusion of predefined subgroup analyses based on EEG measures of the severity of encephalopathy in future clinical trials.

Keywords: Postanoxic encephalopathy, Hypoxic-ischemic encephalopathy, Post cardiac arrest syndrome, Targeted temperature management, Neuroprotection, Resuscitation

☆ Corresponding author at: Medisch Spectrum Twente, Koningsplein 1, 7512 KZ, Enschede, the Netherlands.

E-mail address: s.nutma@mst.nl (S. Nutma).

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Introduction

Anoxic-ischemic encephalopathy is the key determinant of death and disability in comatose patients after cardiac arrest, with in-hospital mortality rates or enduring neurological impairment greater than 50%.1,2 Targeted temperature management (TTM) at 33 °C or 36 °C is applied as a therapeutic strategy in most hospitals to improve neurological recovery, although the clinical evidence supporting efficacy is controversial.3–5 Post-cardiac arrest patients are treated according to fixed protocols, where TTM is initiated as soon as possible after successful resuscitation in all comatose patients, irrespective of the severity of encephalopathy.

Similar outcomes of patients treated with TTM at 33 °C and 36 °C in the landmark TTM trial6 have been discussed extensively. Selective inclusion of patients with relatively mild encephalopathy has been proposed as a possible explanation for the lack of benefit of TTM at 33 °C. This is supported by studies suggesting that TTM at 33 °C might improve outcome of subsets of comatose patients after cardiac arrest with more severe initial brain injury. In one large cohort, beneficial effects of TTM increased with the duration of circulatory arrest, with maximal effects in case of “no-flow times” of over eight minutes.8 A randomized trial showed higher rates of survival and favourable neurological outcome after treatment at 33 °C in patients with cardiac arrest due to non-shockable rhythm.7 A recent cohort study showed lower mortality with treatment at 33 °C in post-cardiac arrest patients with a high Pittsburgh Cardiac Arrest Category (PCAC) illness severity score.8 Another recent study supported this, showing higher rates of good neurologic outcome only in the group with moderate-severity PCAC scores when 33–34 °C was applied.9 Longer no-flow times,10 non-shockable initial heart rhythms,11 and high PCAC scores12 are all well-known predictors of severe encephalopathy.

International guidelines on treatment of comatose patients after cardiac arrest recognize that “whether certain subpopulations may benefit from lower or higher temperatures remains unclear.” To fill that knowledge gap, previous and ongoing clinical trials, such as TTM2 (NCT02908308) and TAME (NCT03114033), include predefined subgroup analyses according to widely-accepted factors, such as reflow time, cause of arrest, and the initial rhythm after cardiac arrest. These are indirect indicators of the severity of encephalopathy. Predefined subgroup analyses based on systematically collected direct measures of baseline encephalopathy are lacking.

Over the past decades, growing evidence supports the use of electro-encephalography (EEG) as a direct measure to quantify the severity of encephalopathy at the bedside.14,15 Various EEG characteristics have been robustly associated with a poor outcome, whereas other aspects showed strong associations with a favorable recovery.14,15 We hypothesize that effects of TTM at 33 or 36 °C depend on baseline encephalopathy as expressed by EEG patterns within 12–24 h after cardiac arrest. We tested this hypothesis by comparing outcomes after 33 vs. 36 °C in three subgroups of patients with mild, moderate, and severe encephalopathy as classified by the EEG, in our prospectively collected multicenter cohort designed to study EEG based outcome prediction after cardiac arrest.

Methods

Design

This is a post hoc analysis of a prospective cohort study on continuous EEG monitoring for outcome prediction of comatose patients after cardiac arrest15, conducted in intensive care units (ICUs) of 5 teaching hospitals in the Netherlands. Patients were included in Medisch Spectrum Twente (Enschede; May 2010 – Nov 2017), Rijnstate Hospital (Arnhem; June 2012 – Oct 2017), St. Antonius Hospital (Nieuwegein; May 2015 – Oct 2017), Universitair Medisch Centrum Groningen (Groningen; Jan 2015 – June 2017), and Vie-Curi Medical Centre (Venlo; March 2016 – Nov 2017). The Medical Ethical Committee Twente approved the protocol and waived the need for informed consent for EEG monitoring and clinical follow-up, because these are part of current care in the participating centers.

Study population

Consecutive, adult (18 years and older), comatose (Glasgow Coma Scale ≤ 8 or suspected in sedated patients) patients after non-traumatic cardiac arrest were included. Exclusion criteria were concomitant acute stroke, traumatic brain injury, or progressive neurodegenerative disease.

Patient characteristics

The following patient characteristics were used for this analysis: age, sex, out-of and in-hospital cardiac arrest (OHCA/IHCA), etiology of arrest (cardiac or non-cardiac), initial heart rhythm (ventricular fibrillation, ventricular tachycardia, pulseless electric activity, asystole, sinus rhythm), EEG patterns and cumulative sedation doses in the first 24 h.

Treatment

Patients were treated according to standard protocols for comatose patients after cardiac arrest. From 2010 to 2014, all patients were treated with targeted temperature management at 33 °C. Following the results of the TTM Trial6, local protocols were gradually adapted in the participating hospitals, where the target temperature was changed from 33 °C to 36 °C. Target temperature was induced as soon as possible after arrival at the emergency room or ICU and maintained for 24 h. Induction was achieved by IV administration of cold saline and cooling pads. After 24 h, passive rewarming was controlled to a speed of 0.25 °C or 0.5 °C per hour. In case of T > 38 °C and a Glasgow Coma Scale score < 8, targeted temperature management was restarted at 36.5–37.5 °C for another 48 h. Sedation was achieved by propofol or midazolam with or without an opioid or sevoflurane/fentanyl. Analgesedation was usually discontinued at a body temperature of 36.5 °C. In all hospitals, a non-depolarizing muscle relaxant (rocuronium or atracurium) was occasionally used in case of severe compensatory shivering.

Decisions on withdrawal of treatment

Withdrawal of treatment was considered ≥72 h after cardiac arrest, during northermthermia, and off sedation. Decisions on treatment withdrawal were based on international guidelines including incomplete
return of brainstem reflexes, treatment-resistant early myoclonus, and bilateral absence of cortical SSEPs.\textsuperscript{14,16} The EEG within 72 h was not taken into account. Infrequently, in case of severe multi-organ failure or absence of cortical SSEPs, withdrawal of treatment respectively based on the severity and prognosis of postanoxic encephalopathy was before 72 h.

**EEG recordings and analyses**

EEG recording and analysis has been described previously.\textsuperscript{15} In short, continuous EEG with 21 electrodes, applied according to the international 10–20 system, started as soon as possible after arrival at the ICU and continued for at least 3 days, or until discharge from the ICU. For practical reasons, EEG recordings were only started between 8 am and 8 pm. All EEG analyses were prespecified and performed offline, after the recordings, blinded to the point in time of the epoch, the patient’s clinical status during the recording, and outcome. Epochs of 5 min were automatically selected by a computer algorithm at 12, 24, 48, and 72 h after cardiac arrest. Epochs with raw EEG data were presented to a reviewer by the computer, in random order. Data were visually classified by 2 reviewers (B.J. R., M.C.T.-C., M.J.A.M.v.P., H.K., A.G., or J.H.), independently. Upon disagreement, consensus was determined by consultation of the examiners who were blinded to the EEG patterns.

**Subgroups based on categorization of EEG at 12 h and 24 h**

For the current analysis, we defined three subgroups of patients with severe, moderate, or mild encephalopathy based on the EEG at 12 or 24 h after cardiac arrest. This subdivision was based on literature and guidelines on the prognostic values of EEG patterns at these time points.\textsuperscript{15–18} Severe encephalopathy was defined as suppressed (<10 $\mu$V), burst-suppression with identical bursts, generalized periodic discharges (GPD) on a suppressed background, low voltage activity (<20 $\mu$V), burst suppression without identical bursts, GPD’s without suppressed background activity, discontinuous and continuous activity.\textsuperscript{15}

**Outcome**

The primary outcome measure was neurologic outcome expressed as the score on the 5-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) at 6 months after cardiac arrest. Outcome was dichotomized as “good” or “poor.” Good outcome was defined as a CPC score of 1 or 2, poor outcome as a score of 3, 4, or 5. CPC scores were obtained by telephone follow-up at 6 months by investigators who were blinded to the EEG patterns.

**Statistical analysis**

Patients were excluded listwise in case of missing data on temperature regimen, EEG at the timepoints 12 or 24 h, and outcome by CPC-scores at 6 months after cardiac arrest. To study the patient characteristics, univariate analyses via T-tests and the Wilcoxon Rank-Sum test were performed.

First, univariate analyses were done to identify the crude relationship between temperature regimen and the dichotomized and non-dichotomized outcome by CPC in the three EEG-based subgroups of the severity of encephalopathy. To this end, the Pearson $\chi^2$ or Fisher exact test was used to test differences in the proportion of patients with a good outcome between 33 °C and 36 °C, per subgroup. P values below 0.05 were considered statistically significant. If needed, we used the Haldane-Anscombe correction to calculate odds ratios. Second, univariate analyses were applied to identify patient characteristics that were possibly associated with the CPC-score. The covariates that showed possible associations with the CPC-scores ($p < 0.10$) were included in a forward multivariate ordinal regression analysis stratified by the severity of encephalopathy. The covariates that showed the most significant relationship with the CPC-scores were added firstly in the multivariate ordinal regression. Based on this model we determined the adjusted common odds ratio’s (acORs) of any shift towards a good outcome on the CPC-scale for 33 °C vs. 36 °C in the three EEG-based subgroups. Since all patients in the severe encephalopathy group had a CPC 5 outcome, this group was excluded from the regression modelling. SPSS 24 (IBM Corp., Armonk, NY) was used for analyses.

**Results**

EEG recordings were started in 902 comatose patients after cardiac arrest. In 42 patients the temperature regimen was unknown. In 370 patients the severity of encephalopathy could not be assessed, because of missing EEG at 12 h or 24 h. Another 11 patients were lost to follow-up, leaving 479 patients for analyses of outcome after TTM 33 °C vs. 36 °C stratified according to the EEG classification [Fig. 1].

**Patient characteristics**

Patient characteristics of the included patients are shown in [Table 2], grouped by temperature regimen. The characteristics of the excluded patients can be found in the supplemental material [ST table 1]. The treatment groups were equal. The CPC-scores at 6 months after cardiac arrest were essentially the same after treatment at 33 °C and 36 °C. Also, the EEG-based categories of the severity of encephalopathy were equally represented in both groups. When taking the whole cohort (n = 902) in consideration, there was no difference in dichotomized outcome when comparing the included with the excluded group (respectively 44.9% vs 47.6% good outcome; $p = 0.446$). Because EEG at 12 h after cardiac arrest was lacking more often in the 36 °C group than in the 33 °C group (37% vs 54%), severity of encephalopathy could be classified in less patients in the 36 °C group than in the 33 °C group (48% vs 67%; $p < 0.001$). The absence of a 12 h EEG was not associated with a different neurological outcome (44% vs 49% good outcome in groups with and without 12 h EEG registration; $p = 0.180$).

**Neurological outcome after 33 °C or 36 °C stratified by the severity of encephalopathy**

All patients with severe encephalopathy had a poor outcome, regardless of treatment at 33 °C or 36 °C. Patients with moderate encephalopathy more often had a good outcome after treatment at 33 °C as compared with 36 °C (66% vs. 45%; OR 2.38, 95%CI 1.32–4.30; $p = 0.004$). Otherwise, in patients with mild encephalopathy, there was no statistically significant difference in the proportion of patients with a good outcome between groups treated at 33 °C and 36 °C (88% vs. 81%; OR 1.68, 95% CI 0.65–4.38; $p = 0.282$). The interaction between the efficacy of TTM regimen and the sever-
ity of encephalopathy was not statistically significant (p = 0.547). The distribution of CPC scores per temperature regimen, stratified by the severity of encephalopathy, is shown in Fig. 2. Ordinal regression analysis showed a shift towards lower CPC-scores at 6 months after TTM 33 °C/C176° vs 36 °C/C176° for moderate encephalopathy (cOR 2.39; 95% CI 1.40–4.08; p = 0.001), but not for mild encephalopathy (cOR 0.81, 95% CI, 0.41–1.59; p = 0.537). [Fig. 3]

Other baseline factors interacting with treatment effect
Corrected for the severity of encephalopathy, the distribution of CPC was significantly better at TTM 33 °C as compared with 36 °C (acOR 1.50; 95% CI 1.02–2.19; p = 0.040). In univariate analyses, the following factors were associated with the odds of a good outcome: cardiac cause of arrest (OR 5.10, 95% CI 3.12–8.36; p < 0.001) and initial rhythm VF (OR 8.14, 95% CI 5.36–12.37; p < 0.001). Adding these factors to our ordinal regression model stratified by the severity of encephalopathy showed no statistically significant change of the interaction between the severity of encephalopathy and treatment effect, indicating that these factors were not independently associated with effect of treatment (acOR for a worse CPC-score at 36 °C in moderate encephalopathy 2.17; 95% CI 1.22–3.88, p = 0.006; acOR for a worse CPC-score at 36 °C in mild encephalopathy 0.73; 95% CI 0.36–1.49, p = 0.389).

Discussion
We show that effects of 33 °C TTM are associated with the severity of encephalopathy in comatose patients after cardiac arrest, with a beneficial effect in moderate encephalopathy and no effect in mild or severe encephalopathy. In case of moderately severe encephalopathy, outcome was better after TTM at 33 °C than at 36 °C. Otherwise, with mild encephalopathy, there was no statistically significant difference in outcome between patients treated at 33 °C and 36 °C. As expected, in patients with severe encephalopathy according to the EEG at 12 or 24 h after cardiac arrest, TTM seems futile. Based on our results, we speculate that associations of TTM effects with other baseline factors, such as cause of arrest and shockability, are probably driven by encephalopathy severity.

This is the first analysis of effects of TTM in subgroups based on direct measures of encephalopathy. Nevertheless, our observed association between improved outcome and TTM at 33 °C in patients with moderately severe encephalopathy is in line with studies showing improved outcome after TTM at 33 °C in patients with long no-flow times, non-shockable rhythms, and high PCAC scores.6–8 Few of the published experimental animal studies or clinical trials on TTM or other neuroprotective strategies have included predefined pathways to healthy outcomes.
Despite pragmatic challenges, we argue for ongoing and easily retrievable direct measures of the severity of encephalopathy, such as EEG, imaging and biochemical measures. Despite pragmatic challenges, we argue for ongoing and future clinical trials to include sufficiently powered, predefined analyses of subgroups based on direct measures of brain damage, such as EEG patterns in the first 24 h, imaging, or neuronal degradation products. Collection of EEG is probably the most pragmatic option, given the possibility of real-time, bedside measurements, and the established predictive value of certain EEG patterns. Inclusion of measures of encephalopathy provides an opportunity to contribute to understanding of effects of neuroprotective treatments, and to transition from untailored to tailored treatment of comatose patients after cardiac arrest.

Our study has obvious limitations. First, this is no randomized trial. Although the temperature regimen was protocolled in all hospitals, we cannot exclude unobserved biases, for example due to gradual changes over time of the population under study or applied treatments other than TTM. Second, there was a selection bias towards assigning the category ‘mild encephalopathy’ more often, the size of the ‘mild encephalopathy’-subgroup in TTM was probably influenced by this selection bias. Third, as in all observational studies on outcome prediction of comatose patients after cardiac arrest, we cannot exclude self-fulfilling prophecy resulting from decisions on withdrawal of life sustaining treatment. Nevertheless, our study supports the notion that the severity of encephalopathy is an important candidate factor determining beneficial or detrimental effects of TTM of comatose patients after cardiac arrest.
CRediT authorship contribution statement

Sjoukje Nutma: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization.

Marleen C. Tjepkema-Cloostermans: Data curation, Writing – review & editing. Barry J. Ruijter: Data curation, Writing – review & editing. Walter M. van den Bergh: Writing – review & editing. Norbert A. Fowler: Writing – review & editing. Francois H.M. Kornips: Writing – review & editing. Gea Drostan: Writing – review & editing. Erik Scholten: Writing – review & editing. Aart Strang: Writing – review & editing. Albertus Beishuizen: Writing – review & editing. Michel J.A.M. van Putten: Conceptualization, Writing – review & editing. Jeannette Hofmeijer: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sjoukje Nutma, PhD candidate, has been paid by funding of ZonMW and Hersenstichting.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.01.026.

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