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Clinical paper

Prognostic significance of clinical seizures after cardiac arrest and target temperature management☆

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ABSTRACT

Aim: Clinical seizures are common after cardiac arrest and predictive of a poor neurological outcome. Seizures may be myoclonic, tonic-clonic or a combination of seizure types. This study reports the incidence and prognostic significance of clinical seizures in the target temperature management (TTM) after cardiac arrest trial. Our hypotheses were that seizures are associated with a poor prognosis and that the incidence of seizures is not affected by the target temperature.
Methods: Post-hoc analysis of reported clinical seizures during day 1–7 in the TTM-trial including their treatment, EEG-findings, and long-term neurological outcome. The trial randomised 939 comatose survivors to TTM at 33 °C or 36 °C with strict criteria for withdrawal of life-sustaining therapies. Sensitivity, specificity and false positive rate for poor outcome were reported for different types of seizures.
Results: Clinical seizures were registered in 268 patients (29%), similarly distributed in both intervention arms. Early and late seizures were equally predictive of poor outcome. Myoclonic seizures were the most common (240 patients, 26%) and the most predictive of a poor outcome (sensitivity 36.1%, false positive rate 4.3%). Two patients with status myoclonus regained consciousness, one with a good neurological outcome, generating a false positive rate of poor outcome of 0.2% (95%CI 0.0–1.0).
Conclusion: Clinical seizures are common after cardiac arrest and indicate poor outcome with limited specificity. Prolonged seizures are a very grave sign but occasional patients may have a good outcome. The level of the target temperature does not affect the prevalence or prognostic significance of seizures.
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Abbreviations: CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; CT, computerised tomography; EEG, electroencephalogram; FPR, false positive rate; GCS, Glascow Coma Scale; ICU, intensive care unit; MRI, magnetic resonance imaging; NSE, neuronspecific enolase; ROSC, return of spontaneous circulation; SSEP, somatosensory evoked potentials; TTM, target tempertaure management; TTM33, TTM at 33 °C; TTM36, TTM at 36 °C; WLST, withdrawal of life-sustaining treatments.

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Introduction

Clinical seizures are common manifestations of neurological injury after cardiac arrest and may be classified as focal or generalised, myoclonic or tonic-clonic or a combination of seizure types.[1] Clinical seizures may or may not be epileptic and other involuntary movements may be misdiagnosed as seizures.[2]

Myoclonic seizures are sudden, brief, involuntary muscle jerks that may be focal, multifocal or generalised, and occur with or without epileptiform activity on the electroencephalogram (EEG).[3–6] Status myoclonus defined as >30 min of generalised myoclonus is a severe form with a grave prognosis.[7,8] Overall, myoclonus is associated with poor prognosis but good outcomes occur.[5,6,9,10] Status myoclonus of early onset (<24 h after cardiac arrest) was previously considered a reliable sign of poor prognosis, but good outcomes have been reported in patients treated with TTM. [5,6,11–13] Action myoclonus persisting after awakening (Lance-Adams syndrome) compatible with otherwise good outcome may occur on rare occasions mainly after cardiac arrest of primarily hypoxic origin.[6,14,15] Tonic-clonic seizures are less common than myoclonic seizures but are also associated with a poor outcome.[16,17]

It is unknown whether post-anoxic electrographic seizures cause further neurological damage or are simply a sign of post-anoxic encephalopathy.[18,19] Since epileptic activity can increase the metabolic rate and thereby inflict further neuronal injury, treatment of clinical seizures is generally recommended.[7,20] These recommendations are based on expert advice awaiting evidence from randomised trials.[21] Myoclonic seizures are often possible to suppress by propofol, but this has not been found to improve outcome.[22]

This post hoc analysis of the Target Temperature Management trial (TTM-trial) reports the incidence and prognostic significance of clinical seizures during the first 7 days in the ICU, interaction with TTM and EEG findings.[23] Our hypotheses were that seizures are associated with a poor prognosis, late occurring seizures are associated with a better prognosis and that the incidence of seizures is not affected by the level of TTM.

Material and methods

Study population

The TTM-trial, was an international, randomised, parallel group, assessor-blinded trial designed to evaluate outcome after temperature management at either 33 °C (TTM33) or 36 °C (TTM36) in unconscious patients after out-of-hospital cardiac arrest of presumed cardiac origin.[23] It enrolled 950 adult (≥18 years) patients in 26 months 2010–2013. The modified intention to treat group included 473 patients at 33 °C and 476 at 36 °C. Trial data were obtained from 36 intensive care units in Europe and Australia with no difference in end-of-trial mortality or 180-day neurological outcome between intervention arms. This post hoc analysis was predefined before the study randomization code was broken.

All patients were sedated, endotracheally intubated and mechanically ventilated. Sedation and neuromusclar blocking agents were not protocolised but sites were instructed to follow their local routines and provide equal treatment for both intervention groups. After ROSC (defined as 20 min of spontaneous circulation) there was a 4 h inclusion window. The intervention period was divided into 3 periods: (a) achievement of target temperature (4 h), (b) maintenance of target temperature (24 h) and (c) rewarming to 37 °C (8 h). After 36 h, sedation was tapered unless continued for medical reasons.

Data collection and definitions

Clinical seizures were reported on a daily basis during day 1–7 in the intensive care unit (ICU). The day of study inclusion was named "day 1". Study inclusion may have taken place at any hour, hence the duration of "day 1" varies.

In the electronic case report form (eCRF) seizures were classified as myoclonic or tonic-clonic, focal or generalised, and duration of seizure as less than or more than 30 min. Treatment of seizures was recorded daily and separately for myoclonic and tonic-clonic seizures. Status myoclonus was defined as generalised (face and extremities) myoclonic convulsions of >30 min duration and tonic-clonic status as generalised tonic-clonic seizures of >30 min duration. Ten patients had incomplete data on seizures entered in the eCRF, these data were retrospectively collected from their medical notes.

The primary outcome was 180-day neurological outcome and secondary outcome was end-of-trial-mortality. Neurological outcome was scored according to the Cerebral Performance Category (CPC) scale. CPC 1–2 was considered good neurological outcome, CPC 3–5 was considered poor neurological outcome.

Formal neuroprognostication was performed 72 h after rewarming in patients who remained unconscious. Strict criteria for withdrawal of life-sustaining therapies (WLST) were applied. These included, but were not restricted to, a therapy resistant electrographic status epilepticus in combination with extensor or absent motor response to pain. Earlier prognostication was allowed for patients with status myoclonus occuring <24 hours after arrest, WLST was permitted if their somatosensory evoked cortical N20 potentials (SSEP) were bilaterally absent after rewarming, in brain death due to cerebral herniation, and for ethical reasons.[24,25]

A routine EEG was performed in patients remaining in coma 12–36 h after rewarming and when clinically indicated. Interpretations of the EEG recordings were done by the local EEG-specialists at the trial sites and reported prospectively in the eCRF as flat background (amplitude <10 μV), continuous background, burst-suppression background, electrographic status epilepticus (repetitive epileptiform discharges with medium frequency >1 Hz appearing continuously for 30 min or in sequences (>10 s) constituting >50% of a 30 min period) or as "other" and specified further in free text. The local EEG-specialists were blinded for level of temperature management. The findings reported in free text were retrospectively categorised by a clinical neurophysiologist (EW) blinded to all clinical data as: flat background; burst-suppression background; continuous background; epileptiform EEG; or as unspecified pattern if not possible to categorise the EEG from available free text data. An epileptiform EEG was liberally defined and included patterns with abundant epileptiform or periodic discharges (in eCRF free text), and electrographic status epilepticus. The description of background pattern in an epileptiform EEG was not collected. EEG reactivity was defined as a reproducible change in frequency or amplitude of the background after sound and pain stimulation and reported in the eCRF as present, absent or not tested.

Statistical analyses

Continuous data are reported as medians and interquartile ranges. Continuous variables were compared by Mann–Whitney-U test. Categorical data were compared using Fisher's exact test or Chi-square as appropriate. In addition, the frequency of seizures in the two temperature groups were compared using a cumulative incidence function with death as a competing event. Survival times were presented as Kaplan–Meier curves and compared using log-rank test. A p-value of <0.05 was considered significant. The

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