

COMMENTARY

Not all rhythmicities and periodicities in coma electroencephalography are fatal—When simplification becomes dangerous

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The multicenter (11 intensive care unit [ICU] centers) TELSTAR Trial,¹ published in *The New England Journal of Medicine* on Feb 24, 2022, with the Title “Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest,” investigated whether intensive, stepwise antiseizure and sedative treatment to suppress rhythmic and periodic patterns (RPPs) found on the electroencephalography (EEG) monitoring would change the outcomes in patients with persistent coma once resuscitated from cardiac arrest (CA). The authors included adult patients monitored with continuous EEG initiated less than 24 h after return of spontaneous circulation (ROSC) and revealing any RPPs. In the “antiseizure group” the authors proposed a step-by-step medication approach with the goal of suppressing all RPPs for at least 48 h (defined as >90% of activity suppressed), with a

treatment onset within 3 h after RPPs detection. The control group was treated with standard care, including the administration of sedative medication if needed for mechanical ventilation or to suppress clinically manifest myoclonus, irrespective of the EEG findings; additional use of antiseizure drugs in this group was discouraged. The primary outcome was a cerebral performance category (CPC) at 3 months defined as “good” with a score of 1–2, or “poor” with a score of 3–5. Mortality, length of stay in the ICU, and duration of mechanical ventilation were defined as secondary outcomes.

Among 172 included patients, aggressive antiseizure treatment as a response to RPPs did not show any difference of the primary and secondary outcomes as compared to the control group.

These results may lead to the conclusion that antiepileptic treatment is useless in all patients with any RPPs following ROSC. According to our assessment, however,

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the results of the study are well explained by the inclusion of any RPP without limiting the study to EEG patterns reflecting status epilepticus (SE).² The TELSTAR trial was announced in 2014³ as a trial aiming to investigate the benefits of aggressive treatment of electrographic status epilepticus (SE) after cardiopulmonary resuscitation. In the recently published study, however, authors included not only EEG patterns reflecting SE, but also low frequency (i.e., 0.5–2.5 Hz) not-evolving RPPs, reflecting more an encephalopathic irreversible condition, than an ictal and thereby potentially reversible one. This ambiguity is confirmed by the adoption of an antiseizure medication protocol based on the international guidelines for the treatment of SE, whereas authors never refer to SE in describing the EEG patterns investigated and “treated.”

In 2014, when the study was started, the new 2021 version of the American Clinical Neurophysiology Society's Standardized Critical Care Terminology² including definite criteria for seizure and SE was not yet published; nevertheless, consensus on SE was already established in 2015 by the International League Against Epilepsy (ILAE),⁴ as well as the consensus for the diagnosis of nonconvulsive status epilepticus (NCSE) as outlined by the Salzburg criteria in 2015.^{5,6} The actual motives for the decision of including any RPP frequencies are, unfortunately, not mentioned by the authors.

Although the authors refer to “proper” electrographic seizures with ≥ 2.5 Hz on EEG in 10% of patients, SE and status myoclonicus were neither reported nor distinguished.

SE post-CA has been investigated extensively and has been an independent predictor of poor prognosis in large cohorts,⁷ especially with seizure-associated motor symptoms (convulsions, myoclonus).^{8–10} Nevertheless, recovery from SE post-CA has been described with good outcome in selected cases.^{11–15} In particular, it appears from the literature that NCSE (i.e., NCSE meaning, electrographic SE in coma⁴) following CA is associated with favorable outcome (CPC 1–2) in up to every fourth patient in 11 studies^{11–13,16–23} (four prospective observational, seven retrospective) of various quality and design describing or indirectly reporting NCSE in this population of patients.

We cannot exclude the possibility that treating post-CA resuscitated patients with sedation and muscle relaxants to control myoclonus or subtle motor symptoms including shivering, would transform a simultaneously present SE with motor symptoms into NCSE. As neither the number of SE nor the type of SE has been reported in this article, it is not known whether conditions with alternating NCSE and SE with motor symptoms can exist in the same patient, and if this might have an impact on outcome.

The majority of patients investigated in the trial showed myoclonus (98/157 patients, 62%), but it is unclear if the myoclonus should be considered in the context of SE with

motor symptoms or status myoclonicus not fulfilling the EEG criteria of SE. This is crucial because it is well described that myoclonus seen with status myoclonicus⁷ is almost invariably associated with bad prognosis and represents a robust predictor of poor outcome, as also mentioned in the most recent 2021 Guidelines of the European Resuscitation Council and European Society of Intensive Care Medicine.²⁴

Another important limitation of this study is the delay with which EEG studies were performed following CA: EEG was initiated within a median of 13.5 h after ROSC, later than in several studies reporting NCSE following CA.^{12,13,16–18,22} With such a delay, missed early NCSE cannot be excluded. In the study from Rittenberger and colleagues in 2012,²² for example, with the main focus on NCSE detection in adult post CA patients, NCSE was detected at the onset of the EEG recording (median of 9 h) in 25% of NCSE patients, indicating that there might have been a substantial proportion of patients in NCSE shortly after ROSC.

In the antiseizure medication group, EEG results were checked every 3 h and treatment introduced within 3 h, quite a large time window, especially with EEG patterns reflecting SE.

Looking more closely at patients with a favorable outcome (8 in the control group and 10 in the antiseizure treatment group), we note that when excluding patients with the 0.5–2.5 Hz-not-evolving generalized periodic discharge patterns (GPDs), 6 of 20 patients presented EEG patterns potentially compatible with SE (electrographic seizure ≥ 2.5 Hz, evolving pattern 0.5–2.5 Hz, and other 0.5–2.5 Hz). These patients had a good outcome if aggressively treated, without greater complications than in controls, whereas all patients in the control group died. Although the limited sample sizes of these subgroups do not allow firm conclusions, they at least question the conclusion that aggressive antiseizure treatment of RPPs on EEG following ROSC is useless in any context (including patients with post-ROSC SE). Another study that further strengthens these concerns reports good outcome in 44% of adult patients with refractory SE emerging from presumed hypoxic-ischemic encephalopathy if aggressively treated.²⁵

In conclusion, we suggest caution when interpreting the results of the TELSTAR study.

We firmly believe that, despite the absence of improvement in outcomes in aggressively treated post-CA comatose patients showing RPPs, those with SE may benefit from treatment, as SE represents a potentially treatable and reversible condition. We therefore strongly suggest close monitoring of comatose post-CA patients after ROSC as soon as possible, enabling the detection and early treatment of NCSE. *“Contradiction is not a sign of falsity, nor the lack of contradiction a sign of truth” (Blaise Pascal).*

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CONFLICT OF INTEREST

Pia De Stefano reports no conflicts of interest.

Peter W. Kaplan has provided unsponsored grand rounds; published books on electroencephalography, status epilepticus, and epilepsy for which he received honoraria; has consulted for Cadwell and Ceribell; has been on the boards of the American Board of Clinical Neuropsychology, the International Congress of Clinical Neurophysiology, and the American Clinical Neurophysiology Society; and has testified on the use of quantitative electroencephalography (qEEG). He received funding from electroencephalography, qEEG, Demos, Wiley-Blackwell, and Ceribell.

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