Editorial

Seizures and status epilepticus in post cardiac arrest syndrome: Therapeutic opportunities to improve outcome or basis to withhold life sustaining therapies?

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Acute coma and disorders of consciousness continue to be among the most challenging problems in patients who are successfully resuscitated with post-cardiac arrest syndrome (PCAS). It is widely acknowledged that therapeutic hypothermia has shifted the outcome paradigm by improving survival and enhancing the functional outcome. The realization that therapeutic hypothermia can ameliorate acute neurologic injury has improved research into other possible neuroprotective strategies in the post-cardiac arrest period. At the bedside, there is a growing awareness of the need to diagnose and treat the neurologic pathologies in the hope of further improving clinical outcomes. Of the many etiologies of acute coma, seizures, especially non-convulsive seizures are common and effective control may result in improved outcomes. Despite the growing awareness, the diagnosis and management of seizures and status epilepticus (SE) continues to be a major problem in PCAS.

A report by Mani et al. entitled: “The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia” helps direct the growing awareness of seizures in PCAS in a positive direction. In this study of 38 comatose PCAS patients treated with therapeutic hypothermia, continuous-EEG-monitoring (cEEG) was initiated as soon as possible after ICU admission. The investigators reported 23% (9/38) of patients had electrographic seizures. Seventy-eight percent (7/9) of seizures were status epilepticus. The median onset of the seizures was 19 h post-arrest and 5/9 (56%) had seizure-onset prior to rewarming. Forty-five percent (17/38) had evidence of epileptiform activity during the first 24 h post-arrest. Electrographic seizures were significantly associated with preceding interictal epileptiform activity. The neurology team interpreted the EEG twice a day but the specific management of seizures was left at the discretion of the primary team. The outcome for those with seizures was poor, with 94% (16/17) having epileptiform activity and 100% (9/9) of patients having electrographic seizures with death or poor neurologic outcome at discharge.

The thoughtful approach to establish useful and universal EEG criteria for diagnosis and treatment of epileptiform activity, seizures and SE in this patient population is a definite strength of the study. Notably, the study of Mani et al. presents several limitations. But taken from another perspective, these limitations may in fact be opportunities, too. The authors took a conservative definition of SE that requires 30 min of seizure duration but the application of the revised definition of seizures duration of ongoing epileptic activity for >5 min may increase the incidence of SE and provide another opportunity for early aggressive treatments that may help with success. The small sample size from a single center is a weakness but the observations generated provide compelling argument for studying larger and more diverse PCAS population. The fact that the presence or absence of early post-return of spontaneous circulation (ROSC) epileptiform activity is unknown (given that cEEG was initiated at 15 h post ROSC) may highlight an opportunity for earlier diagnosis and possibly more effective therapies.

Importantly, Mani et al. also present the opportunity to look at the state of practice and opportunities to improve our approach to seizures and SE in PCAS.

First, this study shows that a significant proportion of epileptic seizures occur during the first 24 h post-arrest while patients are still actively undergoing therapeutic hypothermia and clinical manifestations of seizures may be obscured by medications (i.e. pharmacologic paralysis). This reinforces the need for a multidisciplinary team approach, especially the involvement of the neurology service from the onset of PCAS as well as for prompt EEG monitoring during the early stages of therapeutic hypothermia.

Second, the timing of diagnosis of seizure is critical. While EEG is the only diagnostic tool to establish seizures, it is the early deployment of EEG monitoring with the prompt interpretation and recognition of epileptic activity that leads to the initiation of seizures management. The time of initiation of treatments is critical because the success of effectively controlling seizures falls rapidly as seizures duration progresses from onset. Furthermore, it has been demonstrated for other etiologies of SE that increasing seizure duration itself is associated with higher rates of mortality.

Third, the need to reliably detect epileptiform activity and seizures early supports the use of cEEG as opposed to routine (short duration) EEGs in the setting of PACS. The study by Mani et al. shows that most of the epileptic activity occurs earlier than previously thought. Routine EEG was able to detect seizures in 8% of comatose patients in a general ICU but cEEG is shown to increase detection of seizures up to 48% in a variety of patients groups at risk for seizures, with 52–100% seizures detected as non-convulsive. One study shows the findings generated by cEEG monitoring led to the initiation of antiepileptic therapy in 14% and modification of antiepileptic therapy in 33% of patients.

Fourth, the clinical uncertainty of less established but potentially epileptiform activity on EEG (rhythmic delta waves, low-frequency
GPDs, etc.) presents the need to establish the indication for treat-
ment and define the outcomes of patients with these EEG findings.
Mani et al. suggest that the presence of any frequent epileptiform
activity, not just the presence of seizures serves as an indicator of
poor neurological outcome. This finding merits further investiga-

Fifth, it is important to recognize that effective treatment of SE
of all etiologies, including PCAS is significantly limited by the lack of
well-designed clinical trials. Beyond the only randomized clinical
trial for SE showing the benefit of benzodiazepine as the first line
agent for SE, subsequent interventions after benzodiazepine have
not been truly proven effective in SE. Mani et al. note this limita-
tion with the variability of management of PCAS SE. There is a great
need for well-designed clinical trials of therapies for seizures and
SE in PCAS.

Sixth, SE in PCAS is typically seen as a predictor of poor outcome.
Prognostication studies in the hypothermia treated post-cardiac
arrest patients are fraught with limitations that includes most
importantly – self-fulfilling prophesy. Control of SE in PCAS may
improve clinical outcomes. It is our opinion that epileptiform
activity, seizures and SE in this patient population should be diag-
nosed early and then viewed as an opportunity to develop better
therapeutic strategies to improve outcome rather than establishing
it as a basis for withdrawal of life sustaining measures.

As we attempt to better understand epileptiform activity,
seizures, and SE in PCAS patients, we realize that the problems
are not limited to the timing of EEG testing or the recognition
of seizures, but also the lack of proven effective treatments for
seizures and SE in PCAS. It was not long ago that neuroprotective
trials after cardiac arrest uniformly failed. Many felt that neurologic
outcome in these patients is destined to be poor. But the problem
is so important that some continued and with more thoughtful lab-
atory, translational and clinical research established the role of
therapeutic hypothermia. Now we are faced with a similar prob-
lem, a similar opportunity. There are two ways of looking at seizures
and SE in patients with PCAS: as a prognosticator for poor outcome,
which will almost guarantee a self-fulfilling prophecy or as a chal-
lenge to further develop novel diagnostic approaches and therapies
to improve outcome. The study by Mani et al. shows a starting
point in the positive direction.

Conflict of interest statement

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