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Title: EEG Slow Wave Activity in Hypoxic Brain Injury – A substudy of STEPCARE trial

Short title: PROPEA STEPCARE

Overview

The PROPEA STEPCARE study is a sub-study of the STEPCARE trial in which the effects of two different approaches of sedation and fever management, and two target levels of mean arterial pressure (MAP) on the outcome of out-of-hospital cardiac arrest (OHCA) patients are investigated. It is a continuation of the PROPEA3 study in which the electroencephalogram (EEG) slow wave activity (SWA) was investigated as an early phase prognostic measure for functional outcome after OHCA. In the PROPEA STEPCARE study, we investigate if the time of SWA exceeding a predefined threshold predicts the functional outcome after cardiac arrest (CA) and if the difference in treatment protocols carried out as a part of STEPCARE trial affects the accuracy of outcome prediction. The results are compared to blinded retrospective visual analysis of EEG. The data collection will be carried out in selected centers participating the STEPCARE trial.

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Background and significance

Guidelines recommend multimodal outcome prediction in post-resuscitation care. [1, 2] Assessment including clinical examination, electrophysiologic measurements, biomarkers, and neuroimaging is recommended. [1, 2] In order to avoid inappropriate withdrawal of life-sustaining therapies or futile treatment, accurate methods for prognostication are important. [3]

EEG is commonly used to provide prognostic information to support clinical examination. [4] Specific EEG features have been shown to associate with outcome [5, 6] and may provide valuable prognostic information at an early stage, during and after the first 24 hours after CA. [7, 8] Current ERC guideline recommends EEG after first 24 hours from return of spontaneous circulation (ROSC) for prediction of poor outcome, due to ~~improving~~ increased specificity ~~for poor outcomes~~ after this time point. [8]

Currently, utilization of EEG in the early post-resuscitation care is still ~~not widely adopted~~depending on local routines. Adherence to consensus guidelines may depend on availability of qualified technicians or specially trained nurses and costs related to carrying out recordings especially outside office hours. Furthermore, need for experts with adequate training to interpret intensive care recordings may restrict the use of EEG in post-resuscitation care.

We have recently shown that EEG slow wave activity (SWA) during the first 24 hours is a promising measure for outcome prediction after CA. [9] In the PROPEA3 study, the patients with poor functional outcome had significantly lower SWA measured with C-Trend Index, a parameter provided by commercially available medical device software C-Trend, during the early phase of recovery compared to those with good outcome. A C-trend index cut off value 20 had the best accuracy for predicting poor outcome. The recordings were performed with a disposable self-adhesive frontal electrode and wireless device offering a practical approach for early bedside evaluation of recovery of brain function and prediction of outcome after CA. [9]

The PROPEA STEPCARE is a substudy of STEPCARE, a prospective randomised multicenter ~~study~~ trial in which the effects of two different approaches of sedation and fever management, and two target levels of mean arterial pressure on the outcome of OHCA patients are investigated. We In the PROPEA STEPCARE, we will assess the EEG SWA with C-Trend Index. We will assess the value of time at which C-trend index exceeds a predefined threshold value in predicting the outcome after cardiac arrest. Furthermore, we will evaluate the effect of different treatment protocols carried out as a part of STEPCARE trial on the prediction accuracy. The

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purpose is to investigate further the clinical value of the approach of using EEG SWA as a practical tool for early bedside evaluation of outcome after CA and find out whether how patient is treated in terms of sedation, temperature management, and target level of MAP should be taken in the account in the evaluation. We also compare the prediction accuracy to blinded retrospective visual analysis of EEG.

Hypotheses and outcomes

Our hypothesis ~~is~~ are:

- A ~~that~~ delayed recovery of EEG SWA predicts poor functional outcome ~~of~~ after cardiac arrest ~~patients and~~
- ~~that~~ The prognostic ~~prediction~~ accuracy of EEG SWA is comparable with that of visual analysis of EEG at 48 hours.
- ~~Furthermore, we hypothesize that, how patient is~~ Ttreatmented in terms of sedation, temperature management, and target level of MAP have no effect on the prognostic performance of SWA.
- For the evaluation of delay in the recovery of SWA, the time at which C-Trend Index exceeds the threshold value of 20 after return of spontaneous circulation (ROSC) is used. The value below 20 is considered to represent very low SWA.

Primary study question: What is the accuracy of the time delay between ROSC and the time when C-Trend Index exceeds 20 in predicting patient outcomes after cardiac arrest.

Secondary study question: Is the predictive accuracy of the time delay between ROSC and the time when C-trend exceeds 20 affected by the three different treatment protocols (sedation, temperature management, target level of MAP).

*Exploratory study questions: C-Trend Index in reference to the neuropsychological outcome? *

For patient outcome, two dichotomous measures are used: ICU mortality as an early measure and functional outcome assessed using the modified Rankin Scale (mRS) at 6 months after cardiac arrest (4-6 representing poor outcome) as the main measure.

Data collection

The data collection will be carried out in selected centers participating the STEPCARE trial. The inclusion and exclusion criteria of STEPCARE trial will be applied. In addition, patients with significant pre-existing neurological comorbidity (e.g. Alzheimer's disease or other progressive memory disorder, poorly controlled epilepsy or stroke with significant functional impairment), foreign citizens, pregnant or lactating patients, and patients under coercive measures will be excluded. In total, 200 patients will be recruited.

The management in the ICU is according to the STEPCARE trial protocol. A continuous EEG recording will be initiated as soon as possible after admission to the ICU and continued until 48 h from ROSC or until the patient awakens to obey verbal commands, whichever comes first. The recording is carried out with a disposable self-adhesive BrainStatus electrode attached to the forehead of the patient including 10 EEG channels (Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9, and T10) and a wireless recording device (Bittium Oyj, Oulu, Finland). Furthermore, four additional cup electrodes (C5, C6, O1, and O2) may be used if considered necessary by the treating clinicians. Electrode placement and initiation of recording are performed by a study nurse or trained ICU nurse according to written instructions. In case of need for electric cardioversion or CT scan, the personnel are instructed to detach the recording device from the electrode. For magnetic resonance imaging

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(MRI), also the electrode is removed. The C-Trend parameters (C-Trend Index, BSR, aEEG, and ADR) are provided online by the BrainStatus platform. Continuous standard EEG is visible on the BrainStatus monitor in sites that use continuous EEG for routine monitoring of CA patients and may be used for prediction of neurological outcome. However, all clinical and research personnel are blinded to the C-Trend parameters. The data are collected to the xxx and transferred to yyy in zzz. The C-Trend data will be analysed by independent members of the research team blinded to the clinical outcome data, after all the surviving participants have been evaluated six months after the CA.

The EEG recordings at 48 hours after ROSC are visually analysed in terms of highly malignant patterns referring to poor outcome.

The outcome of the patients is evaluated with two dichotomized measures. The main evaluation is performed after a 6-month follow-up period from cardiac arrest with mRS where scores 1-3 represents good and 4-6 poor outcome. The mRS-based evaluation is a part of the STEPCARE study protocol. The second measure is ICU mortality. The patients may also go through a separate testing for neuropsychological outcome.

Statistical plan and data analysis

Primary study question

The accuracy of the time at which C-Trend Index exceeds the threshold of 20 after ROSC in predicting the poor outcome of cardiac arrest survivors is evaluated. For the accuracy measures, area under the receiver operating characteristics curve (AUCROC), sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) with confidence intervals are used. The time at which the C-Trend Index value exceeds 20 is defined as the moment in which the average C-Trend Index value calculated automatically over a one-hour time window first exceeds 20. Furthermore, the prediction accuracy is statistically compared to that of blinded retrospective visual analysis of highly malignant EEG patterns at 48 hours from ROSC. *How?*

Secondary study questions

The effect of the three different treatment protocols of STEPCARE trial (sedation, temperature management, target level of MAP) on the accuracy measures described above is evaluated. The accuracy measures are statistically compared between the two groups of sedation, temperature management, and target level of MAP. *How?*

Secondary study questions

The effect of propofol infusion rate, body temperature, and MAP on the accuracy measures described above is evaluated. The contribution of these three factors in the accuracy measures are statistically compared. *How?*

References

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3. Amorim E, Mo SS, Palacios S, et al. Cost-effectiveness analysis of multimodal prognostication in cardiac arrest with EEG monitoring. Neurology 2020; 95:e56375.

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Commented [JH(11]: I added this to the protocol to keep the blinding until final analysis, ok?

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