RESUSCITATION 143 (2019) 17–21

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Short paper

Stratifying comatose postanoxic patients for somatosensory evoked potentials using routine EEG

A. Fredland, S. Backman, E. Westhall *

Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Clinical Neurophysiology, Lund, Sweden

Abstract

Introduction: Multimodal neurological prognostication is recommended for comatose patients after cardiac arrest. The absence of cortical N20-potentials in a somatosensory evoked potential (SSEP) examination reliably predicts poor outcome, but presence of N20-potentials have limited prognostic value. A benign routine electroencephalogram (EEG) may identify patients with a favourable prognosis who are likely to have present N20-potentials.

Objective: To investigate whether a routine EEG can identify patients where SSEP is unnecessary to perform.

Methods: In a multi-centre trial, comatose patients after cardiac arrest were randomised to a controlled temperature of 33 °C or 36 °C. A routine EEG was protocolised and SSEP performed at the clinicians' discretion, both during normothermic conditions. EEGs were categorised into benign, malignant or highly malignant based on standardised terminology. A benign EEG was defined as a continuous normal-voltage background without abundant discharges. The N20-potentials were reported as absent (bilaterally) or present (bilaterally or unilaterally).

Results: Both EEG and SSEP were performed in 161 patients. EEG was performed before SSEP in 60%. A benign EEG was seen in 29 patients and 100% (CI 88–100%) had present N20-potentials. For the 69 patients with a malignant EEG and the 63 patients with a highly malignant EEG, 67% (CI 55–77%) and 44% (CI 33–57%) had present N20-potentials, respectively.

Conclusions: All patients with a benign EEG had present N20-potentials, suggesting that SSEP may be omitted in these patients to save resources. SSEP is useful in patients with a malignant or highly malignant EEG since these patterns are associated with both present and absent N20-potentials.

Keywords: Cardiac arrest, EEG, SSEP, Prognosis, Coma

Introduction

EEG is a commonly used tool to assess brain function in comatose patients resuscitated after a cardiac arrest (CA).[1] A classification of benign, malignant and highly malignant EEG patterns have previously been proposed.[2] A benign EEG may identify patients with a good prognosis.[3]

Somatosensory evoked potentials (SSEP) is an important method for predicting poor prognosis.[4,5] If cortical N20-potentials are absent bilaterally the prognosis is poor with specificities close to 100%.[4,6] SSEP is less available compared to EEG[1] and its sensitivity to predict a poor outcome is limited.[7]

A clinically relevant question is whether to perform SSEP in all patients or not. Previous studies have evaluated SSEP in addition to EEG to predict poor outcome.[6,8] One study explored if clinical data and EEG could predict absence of N20-potentials,[9] but no study has investigated if a benign EEG can be used to anticipate presence of N20-potentials. The aim of this study was to investigate if a routine EEG can identify patients where SSEP is unnecessary to perform.

Methods

In the Targeted Temperature Management (TTM) Trial, 939 adult comatose patients following an out-of-hospital CA were randomised to

Abbreviations: CA, cardiac arrest; CI, 95% Confidence interval; EEG, electroencephalography; IQR, interquartile range; SSEP, somatosensory evoked potentials; TTM, targeted temperature management.

* Corresponding author at: Department of Clinical Neurophysiology Skane University Hospital, S-221 85 Lund, Sweden.
E-mail addresses: anna.fredland.607@student.lu.se (A. Fredland), sofia.backman@med.lu.se (S. Backman), erik.westhall@med.lu.se (E. Westhall).

https://doi.org/10.1016/j.resuscitation.2019.07.027
Received 12 June 2019; Received in revised form 10 July 2019; Accepted 26 July 2019

two different temperature treatments (33 °C or 36 °C). The trial was granted by the ethics committees in each participating country.[10]

Consecutive patients at the 36 sites were included in the present study if both EEG and SSEP were performed within 10 days after CA. According to the trial protocol[11] a routine EEG was mandatory to be performed in patients still unconscious 12–36 h after rewarming or later due to weekends. The EEGs were retrospectively analysed in a blinded fashion by experienced EEG experts and classified according to predefined categories based on the American Clinical Neurophysiology Society's EEG terminology:

Highly malignant patterns

- Suppressed background (<10 μV) without discharges
- Suppressed background with superimposed periodic discharges
- Burst–suppression (suppression ≥50%)

Malignant features

- Abundant periodic discharges or rhythmic polyspike-/spike-/sharp-and-wave (≥50%)
- Discontinuous background (suppression 10–49%)
- Low-voltage background (10–20 μV)
- Reversed anterio-posterior gradient

Benign pattern

- Continuous normal-voltage background without any malignant features

A published study protocol describes the management of the EEGs in the TTM-trial.[2] According to the TTM-trial protocol[11] a median nerve SSEP was recommended in unconscious patients at 48–72 h after rewarming, but not mandatory and performed at the clinicians' discretion. For patients with an early clinically defined status myoclonus, SSEP could be performed directly after rewarming. The results were documented as N20-potentials absent (bilaterally) or present (unilaterally or bilaterally) according to the local SSEP-report and no uniform criteria for N20-amplitudes or acceptable noise level were introduced in the trial. Parts of the EEG data as well as the SSEP results have previously been published,[3,12,13] but no comparisons between these methods have been made.

SPSS version 25.0 was used for Chi-square test or Fisher's exact test where applicable. Wilson score interval was used to determine 95% confidence intervals for percentages. Data is presented as mean value with standard deviation or as median and interquartile range.

Results

Patients

161 patients from 15 sites had performed both routine EEGs and SSEP and were included in the present study (Fig. 1). The cohort was divided into three EEG categories, benign (n = 29), malignant (n = 69) or highly malignant (n = 63). Patient characteristics and CA related variables are presented in supplementary tables S1 and S2.

EEG and SSEP results

Table 1 presents the SSEP results in each EEG category. A benign EEG defined as a continuous normal-voltage background and absence of abundant discharges was seen in 29 patients (18%). All the patients with a benign EEG had present N20-potentials with a relatively narrow confidence interval (CI 88–100%). In the malignant EEG category 67% (CI 55–77%) had present N20-potentials compared to 44% (CI 33–57%) in the highly malignant EEG category. There was a statistically significant difference regarding the presence of N20-potentials between the benign and the malignant EEG category ($p < 0.001$) as well as between the malignant and the highly malignant group ($p = 0.01$). The long-term neurological outcome for each EEG group is presented in supplementary Table S2.

EEG reactivity

Reactivity was not included in the definition of a benign EEG. In the benign group, notations regarding reactivity testing were available in 18 patients (62%). Among those, reactivity was present in 10 patients, absent in four and unclear in four patients.

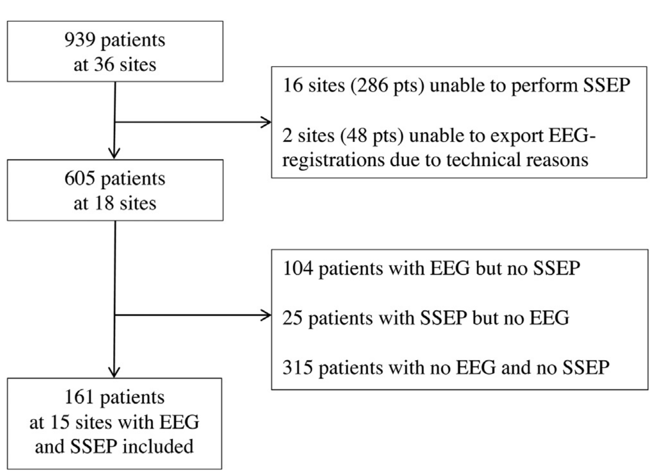

Fig. 1 – Flow chart of the inclusion of patients in the study.

Table 1 – EEG categories in relation to SSEP results.

	Benign EEG (n = 29)	Malignant EEG (n = 69)	Highly malignant EEG (n = 63)
Present SSEP, n	29	46	28
Present SSEP, % (95% CI)	100 (88–100)	67 (55–77)	44 (33–57)

Present SSEP was defined as present median nerve cortical N20-potentials unilaterally or bilaterally. There was a highly significant difference ($p < 0.001$) in prevalence of N20-potentials between the benign and the malignant EEG category and a significant difference ($p = 0.010$) between the malignant and the highly malignant category.

Time-points of EEG and SSEP

The duration from CA to performance of EEG and SSEP are presented in Fig. 2. The majority of the EEG registrations (60%) were performed before SSEP. The duration from arrest to EEG and SSEP were similar in the different EEG categories (Suppl Table S2).

Discussion

Neurophysiological methods are included in algorithms for prognostication following CA,[4,5] but questions remain regarding their most efficient usage. In this cohort, we showed that all patients with a benign EEG had present N20-potentials. Since a benign EEG can predict presence of N20-potentials we suggest that SSEP does not need to be performed in this subgroup of patients. We base this assumption on the traditional view that present N20-potentials is a poor indicator of a good outcome but we are aware that further development of the SSEP-technique may change the scenario. Recent studies suggest that normal N20-potentials with amplitudes above a certain threshold[14] or analysis of high frequency components of the cortical SSEP response[15] may provide information about a likely favourable outcome. Whether SSEP with more detailed analyses provide additional prognostic information compared to a benign EEG was outside the scope of our study since we had limited access to the original SSEP signals.

The definition of a benign EEG includes a continuous normal-voltage EEG background, which has been demonstrated in several studies to predict a good outcome.[3,6,12] We chose not to include a reactive background in the definition of a benign EEG since many sites were unable to export notations regarding reactivity. The benign EEG category therefore included EEGs with present, absent or unknown reactivity. Nevertheless, all EEGs classified as benign predicted presence of N20-potentials.

In the malignant and highly malignant EEG categories the percentage of poor outcome was high, 87% and 98%, respectively. These EEG patterns could not predict the SSEP results for the individual patient. The finding of absent N20-potentials adds important prognostic information to confirm severe brain injury, since false positives cannot be excluded with EEG, and a combination of several methods are recommended to predict poor prognosis.[4,13]

We found a higher percentage of patients with poor outcome despite a benign EEG, 38%, compared to our previous reports from the TTM-trial.[3,12] This may be due to a selection bias since SSEP was performed at the discretion of the treating physician and not mandated by the protocol. Further, patients that woke up early after rewarming and weaning of sedation did not require EEG or SSEP and were thus excluded from the present study.

The absence of N20-potentials or absent pupillary and corneal reflexes are considered the most robust methods in predicting poor outcome.[4,5] The electrophysiological methods are not recommended for prognostic purposes during the first 48 h after CA due to the potential influence of sedation and hypothermia, but there are no exact recommendations regarding the optimal time-points or in which order to perform EEG or SSEP. Whereas SSEP is less sensitive to the effects of sedation, EEG may provide important information about on-going electrographic seizures. Although some patients with a good outcome may have a grossly pathological EEG very early after CA, there is growing evidence that strictly defined EEG patterns, such as burst–suppression with identical bursts, reliably predict poor outcome independent of the time-point of performance.[6]

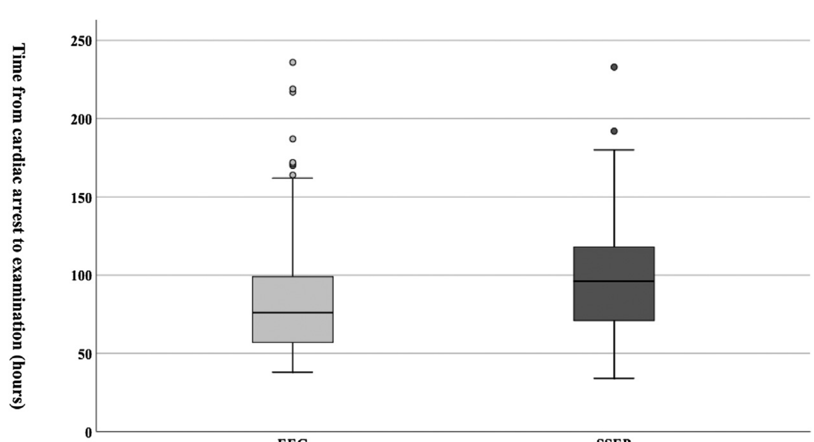

Fig. 2 – The duration (hours) from the cardiac arrest to the performance of EEG and SSEP in the cohort (n = 161). Median duration to EEG was 76 h (IQR 57–99, range 38-236). Median duration to SSEP was 96 h (IQR 71–118, range 34-233).

In this multi-centre study the majority of patients had EEG performed before SSEP and we suggest to use EEG to stratify patients for SSEP. In patients with a benign EEG pattern SSEP could be omitted or postponed, thus saving resources by avoiding unnecessary investigations.

Strengths with this study is that data was obtained from the multi-centre and prospective TTM-trial with a strict protocol for prognostication.[11] The EEGs in the trial were analysed blinded to all clinical data. In addition, this study is less likely to be affected by the self-fulfilling prophecy since primary analysis did not involve outcome, but rather the relation between the results of EEG and SSEP.

Local clinical SSEP reports were prospectively reported and the interpretation was not blinded to the information in the SSEP referral and no uniform criteria for N20-amplitudes or acceptable noise levels were used, which are limitations in this study. The original SSEP signals could not be collected from all sites, mainly due to technical difficulties with the export. There was a limited number of patients with both EEG and SSEP performed, resulting in limited power for the EEG subcategories.

To tailor a multimodal prognostic algorithm further, other markers of good prognosis can be considered, such as low levels of biomarkers in serum or identification of an early continuous background activity using continuous EEG-monitoring.

Conclusions

In this cohort, benign EEGs were always associated with present N20-potentials. A routine EEG could therefore be used to identify the patients where SSEP is of limited prognostic use.

Funding source

The Swedish Heart and Lung Association; the Skåne University Hospital Foundations; the Gyllenstierna-Krapperup Foundation; the Segerfalk foundation; the Swedish National Health System (ALF); the County Council of Skåne; the Swedish Society of Medicine; the Koch Foundation, The Swedish Heart-Lung Foundation, AFA Insurance, The Swedish Research Council and Hans-Gabriel and Alice Trolle-Wachtmeister Foundation; all in Sweden. The Tryg Foundation; Denmark. EU programme Interreg IV A.

Statistical analysis

Susann Ullén, statistician at our institution, advised the statistical analysis.

Authors' contributions

All authors contributed to the conceptualization and methodology of the study. AF and EW performed the formal analysis and wrote the first draft of the manuscript. All authors critically reviewed and accepted the final manuscript.

Disclosures

The authors have no disclosures to report.

Declaration of conflicts of interest

None.

Acknowledgements

We would like to acknowledge the 15 sites that contributed data, site investigators (SI) and the contacts of the EEG-laboratories: Copenhagen University Hospital Rigshospitalet (Christian Hassager SI, Jesper Kjaergaard SI, Michael Wanscher SI, Troels Wesenberg Kjaer EEG), Denmark; Santa Maria degli Angeli Hospital Pordenone (Tommaso Pellis SI), Trieste (Vincenzo Campanile SI), Italy; Centre Hospitalier de Luxembourg (Pascal Stammet SI, Stefan Beyenburg EEG), Luxembourg; Academisch Medisch Center (Janneke Horn SI, Anne-Fleur van Rootselaar EEG), Leeuwarden Medisch Centrum (Michael Kuiper SI, Jan Koornstra EEG), The Netherlands; Haukeland University Hospital Bergen (Jørund Langørgen SI, Harald Aurlien EEG), Norway; Skane University Hospital Lund (Malin Rundgren SI), Skane University Hospital Malmö (Johan Undén SI), Helsingborg Hospital (Jesper Johnsson SI), Örebro University Hospital (Stefan Persson SI, Gunilla Ahlsén EEG), Linköping University Hospital (Nicholas Wyon SI, Hans Lindehammar EEG), Sweden; Geneva (Yvan Gasche SI), St Gallen (Gian-Reto Kleger SI, Dominique Flügel EEG), Switzerland; Guys and St Thomas London (Guy Glower SI, Michalis Koutroumanidis EEG), United Kingdom; Principal investigator of the TTM trial Niklas Nielsen, Sweden; Senior investigator of the TTM trial Hans Friberg, Sweden.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.07.027.

REFERENCES

1. Friberg H, Cronberg T, Dunser MW, Duranteau J, Horn J, Oddo M. Survey on current practices for neurological prognostication after cardiac arrest. Resuscitation 2015;90:158–62.
2. Westhall E, Rosen I, Rossetti AO, et al. Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design. BMC Neurol 2014;14:159.
3. Backman S, Cronberg T, Friberg H, et al. Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the Target Temperature Management trial. Resuscitation 2018;131:24–8.
4. Callaway CW, Soar J, Aibiki M, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2015;132(16 Suppl. 1):S84–S145.
5. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 2014;40(12):1816–31.
6. Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85(2):137–43.
7. Zandbergen EG, Koelman JH, de Haan RJ, Hijdra A. SSEPs and prognosis in postanoxic coma: only short or also long latency responses? Neurology 2006;67(4):583–6.

8. Tsetsou S, Novy J, Pfeiffer C, Oddo M, Rossetti AO. Multimodal outcome prognostication after cardiac arrest and targeted temperature management: analysis at 36 degrees C. Neurocrit Care 2018;28(1):104–9.
9. Daubin C, Guillotin D, Etard O, et al. A clinical and EEG scoring system that predicts early cortical response (N20) to somatosensory evoked potentials and outcome after cardiac arrest. BMC Cardiovasc Disorders 2008;8:35.
10. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 2013;369(23):2197–206.
11. Nielsen N, Wetterslev J, al-Subaie N, et al. Target Temperature Management after out-of-hospital cardiac arrest–a randomized, parallel-group, assessor-blinded clinical trial–rationale and design. Am Heart J 2012;163(4):541–8.
12. Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016;86(16):1482–90.
13. Dragancea I, Horn J, Kuiper M, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33 degrees C versus 36 degrees C: Results from a randomised controlled clinical trial. Resuscitation 2015;93:164–70.
14. Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: a prospective cohort study. Neurology 2015;85(20):1752–60.
15. Endisch C, Waterstraat G, Storm C, Ploner CJ, Curio G, Leithner C. Cortical somatosensory evoked high-frequency (600Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation. Clin Neurophysiol 2016;127(7):2561–9.