Towards multimodal brain monitoring in asphyxiated newborns with amplitude-integrated EEG and simultaneous somatosensory evoked potentials

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Highlights:

- Somatosensory evoked potentials (SEPs) predict outcome after perinatal asphyxia
- SEPs can be recorded with the standard 4-electrode aEEG brain monitoring setup
- aEEG-SEP enables multimodal neurophysiological brain monitoring in the NICU

ABSTRACT

Background: Somatosensory evoked potentials (SEPs) offer an additional bedside tool for outcome prediction after perinatal asphyxia.

Aims: To assess the reliability of SEPs recorded with bifrontoparietal amplitude-integrated electroencephalography (aEEG) brain monitoring setup for outcome prediction in asphyxiated newborns undergoing therapeutic hypothermia.

Study design: Retrospective observational single-center study.

Subjects: 27 consecutive asphyxiated full- or near-term newborns (25 under hypothermia) that underwent median nerve aEEG-SEPs as part of their clinical evaluation at the neonatal intensive care unit of Helsinki University Hospital.

Outcome measures: aEEG-SEP classification (present, absent or unreliable) was compared to classification of SEPs recorded with a full EEG montage (EEG-SEP), and outcome determined from medical records at approximately 12-months-age. Unfavorable outcome included death, cerebral palsy, or severe epilepsy.

Results: The aEEG-SEP and EEG-SEP classifications were concordant in 21 of the 22 newborns with both recordings available. All five newborns with bilaterally absent aEEG-SEPs had absent EEG-SEPs and the four with outcome information available had an unfavorable outcome (one was lost to follow-up). Of the newborns with aEEG-SEPs present, all with follow-up exams available had bilaterally present EEG-SEPs and a favorable outcome (one was lost to follow-up). One newborn with unilaterally absent aEEG-SEP at 25 hours of age had bilaterally present EEG-SEPs on the next day, and a favorable outcome.

Conclusions: aEEG-SEPs recorded during therapeutic hypothermia on the first postnatal days are reliable for assessing brain injury severity. Adding SEP into routine aEEG brain monitoring offers an additional tool for very early outcome prediction after birth asphyxia.

Keywords: Amplitude-integrated electroencephalography (aEEG); Asphyxia; Brain monitoring; Electroencephalography (EEG); Newborn; Somatosensory Evoked Potentials (SEPs)

Abbreviations: aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; HIE, hypoxic-ischaemic encephalopathy; NICU, neonatal intensive care unit; SEP, somatosensory evoked potential; TH, therapeutic hypothermia

INTRODUCTION

Though therapeutic hypothermia (TH) significantly improves outcome after moderate-to-severe perinatal hypoxic-ischaemic encephalopathy (HIE), many of the affected newborns still die in the neonatal period or develop with severe disabilities [1]. The severity of brain injury is difficult to determine during the first postnatal days - particularly in the era of therapeutic hypothermia (TH), which delays early prognostication possibilities with amplitude-integrated EEG (aEEG) [2–7]. Hence, additional prognostic methods are needed particularly during the first two postnatal days to allow informed treatment decisions and parental guidance.

Recent studies in newborns with HIE suggest that somatosensory evoked potentials (SEP) offer an additional method for early outcome prediction at bedside even during hypothermia [8,9] and that SEPs can also be evaluated using the commonly applied bifrontoparietal aEEG brain monitoring montage [10]. Combined recording of SEPs with EEG has several advantages to applying either technique in isolation: i) the simultaneous EEG enables evaluation of SEP with knowledge of the EEG background, and elimination of periods with seizures from the SEP averages. ii) Due to their resistance to hypothermia, SEPs provide an indication of the severity of brain injury during the first two days, when aEEG/EEG based prognostication is limited. Combining SEPs to aEEG brain monitoring could further eliminate the current constraint of neonatal SEPs being limited to office hours. To date there are, however, no studies recording SEPs in the neonatal intensive care unit (NICU) with the routine aEEG brain monitoring equipment

and setup. The previous study evaluating SEPs with an aEEG montage used remontaging for analysis purposes, whereas the data were recorded with a full EEG montage [10].

Therefore, we set out to study the reliability of combining the routine 4-electrode aEEG with SEPs (aEEG-SEP) for outcome prediction in the challenging NICU setting in asphyxiated newborns. Based on previous literature, we hypothesized that the aEEG-SEP results would be comparable to those recorded with a full EEG montage [10] and, consequently, that absent aEEG-SEPs would be associated with a poor outcome and bilaterally present responses with a favorable outcome [8].

PATIENTS AND METHODS

Participants

The study group consists of a systematic retrospective collection of 27 asphyxiated newborns (13 females, gestational age (GA) between 35+0 and 42+1 weeks; for patient details see Table 1) that underwent aEEG-SEPs at the tertiary level NICU of the Helsinki University Hospital between January 2017 and September 2018. Of the 27 newborns, 25 underwent whole-body TH with target temperature 33-34 degrees for 72 hours as part of their treatment strategy (criteria for cooling as in [11]) and all 25 were still under hypothermia during the aEEG-SEP recording. Newborns with genetic abnormalities, inborn errors of metabolism, or major malformations were excluded from the analyses regarding outcome prediction but were included in the analyses comparing the aEEG-SEP and EEG-SEP classification. All neurophysiological recordings were done for clinical indications. The Institutional Research Review Board at HUS Medical Imaging

Center, Helsinki University Hospital approved the study, including waiver of consent due to the retrospective and observational nature of the study.

Decisions on withdrawal of treatment

Decisions to withdraw intensive care were made after discussions with parents and were based on a combination of poor clinical condition including severe HIE, poor aEEG/EEG, and severe MRI findings.

aEEG and aEEG-SEP: Recording and Data analysis

The aEEG recordings were started according to clinical need as soon after birth as possible (median 3 hours, interquartal range, IQR 1 hour). The aEEG was collected from four needle electrodes at F3, F4, P3 and P4 locations at 256 Hz (except during SEP recording at 2000 Hz) using a NicoletOne system (Cardinal Healthcare/Natus, USA). The aEEG-SEP recording was performed according to our in-house developed clinical routines [8,10]. During the aEEG recording, each median nerve was stimulated at the wrist (at a median postnatal age of 24,5 hours, IQR 27,5 hours), with surface electrodes and a portable electrical peripheral nerve stimulator (Micromed Energy Light stimulator; Micromed, Italy), and with current individually adjusted to just above the motor threshold. If standard stimulation at the wrist was not possible due to intravenous or intra-arterial lines, the median nerve was stimulated at the palm.

Two EEG experts (PN and VM) scored the aEEG background activity hour by hour, using the raw 4-channel EEG and the aEEG traces. In case of disagreement, a third EEG

expert (LL) scored the given hour and the three then reached consensus through discussion. The aEEG background categories were: grade 4 = inactive (background activity <10 μV or severe discontinuity meaning interburst interval (IBI) > 60 s), grade 3 = burst suppression (IBI 10 — 60 s, amplitude during suppression < 10 uV, no sleep-wake cycle), grade 2 = continuous activity without clear sleep-wake cycling, grade 1 = continuous activity with recovered sleep-wake cycling (discontinuity allowed during quiet sleep). Each hour received the grade that was present > 50% of the time. Grade 1 started from the hour with the first sleep cycle of at least two consecutive cycles. When artefacts or seizures occupied over 50% of a given hour, no separate background score was assigned. Seizures were defined as rhythmic, evolving EEG patterns lasting longer than 30 s and not explained by artefacts.

We averaged the aEEG-SEPs offline in BESA® software (BESA GmbH, Germany) for epochs between –100 ms and 800 ms relative to stimulus, after discarding periods with seizures from the averages. To reduce artifacts, due to e.g. large movement, we also discarded epochs with amplitude over 200 or 300 uV (depending on the individual amplitude level of the brain activity). To ensure reproducibility of the responses, we averaged the odd and even stimuli separately in addition to the full averages. Two neurophysiologists (PN and LL) classified the early cortical SEPs to be present (a clear peak 15–100 ms post-stimulus), absent, or unreliable (e.g. continuous seizures during stimulation, or no clear response when using stimulation site other than the wrist). The concordance of SEP classification between the two neurophysiologists was 100%.

EEG and EEG-SEP: Recording and Data analysis

Most newborns underwent follow-up EEG-SEP studies between postnatal days one and six (for details of the EEG-SEP protocol see [8]). Two EEG experts (PN and VM) classified the EEG background according to previously described criteria [8] (modified from [12]), and marked the seizures in the same way as for aEEG. In case of disagreement, a third EEG expert (LL) scored the given EEG and the three then reached consensus through discussion. Two neurophysiologists (PN and LL) classified the EEG-SEPs as absent, present, or unreliable (e.g. continuous seizures during stimulation). The concordance of SEP classification between the two neurophysiologists was 100%.

Magnetic resonance imaging (MRI)

All newborns underwent brain MRI between postnatal days two and six [1.5Tesla, Philips Intera Achieva, Philips Medical Systems, Best, The Netherlands (1 newborn), 1.5Tesla Siemens Magnetom Avanto (10 newborns), or 3Tesla Siemens, Magnetom Skyra (26 newborns), Siemens Healthcare GmbH, Erlangen, Germany] with a clinical imaging protocol including T1-weighted axial, T2-weighted axial and coronal, diffusion weighted axial images. An experienced pediatric neuroradiologist (author STS) classified the MRIs into six categories according to previously published criteria [13]. Score 0 = normal. 1A = minimal cerebral lesions and 1B = more extensive cerebral lesions alone (no involvement of basal ganglia, thalamus or anterior or posterior limb of the internal capsule, and no area of watershed infarction). 2A = any involvement of the basal ganglia, thalamus, anterior or posterior limb of the internal capsule or watershed infarction (no

other cerebral lesions) and 2B = 2A + additional cerebral lesions. 3 = cerebral hemispheric devastation.

Outcome evaluation

We determined the clinical outcomes of the surviving newborns retrospectively by review of the medical records, primarily from the follow-up visit to a neuropediatrician or neonatologist at 9- to 18-months age. In five newborns we used 3-months (two newborns) or 6-months (three newborns) visits: In three of them the hospital follow-ups were discontinued at that time due to favourable recovery as newborns and normal development so far, whereas two moved to another hospital district, but so far had had normal development. The predifined outcome categories were i) favorable (normal development or mild abnormality including mild speech, or motor delay) and ii) unfavorable (cerebral palsy, severe epilepsy, and death).

Statistics

We calculated the accuracy, sensitivity, specificity, and positive and negative predictive values, including corresponding 95% confidence intervals, for absent SEPs to predict poor outcome.

RESULTS

We excluded data of one newborn from all analyses, because the aEEG-SEPs were bilaterally unreliable due to continuous seizures during stimulation, and no follow-up EEG-SEP recording was available. Hence, the final study group included 26 newborns.

Concordance between aEEG-SEP and EEG-SEP (Figure 1)

Both aEEG-SEPs and EEG-SEPs were available for 22 newborns. The remaining four newborns had bilaterally present aEEG-SEPs and did not undergo an EEG-SEP as it was not indicated due to fast clinical recovery.

The aEEG-SEP and EEG-SEP results were concordant in all but one of the 22 newborns (95%). EEG-SEPs were bilaterally present in all newborns with aEEG-SEPs bilaterally present (n=14). EEG-SEPs were bilaterally present also in two patients in whom the aEEG-SEP could be reliably evaluated only on one side: in one of them the stimulation site was unusual and the other had continuous seizures. In the only newborn with only unilaterally present aEEG-SEP recorded on the first postnatal day, the follow-up EEG-SEPs were bilaterally present on the following day. Finally, the follow-up EEG-SEPs were absent in all the five newborns with bilaterally absent aEEG-SEPs.

Neurophysiological measures and outcome

Table 2 shows the predictive values of aEEG-SEP findings for unfavorable outcome. One newborn with a genetic disorder was excluded from the outcome prediction analysis (patient 6 in Figure 2).

All newborns with aEEG-SEPs present, and follow-up information available (n=19) had a favorable outcome (one was lost to follow-up). The aEEG background at the time of the aEEG-SEP was continuous in all but one of these newborns (patient 25 in Figure 2), but

sleep-wake cycling had not yet recovered in eight (Figure 2). The MRI was normal in 15 of these newborns, whereas four had mild-to-moderate MRI abnormalities (score 1A, 1B, or 2A; Figure 2).

Of the five newborns with bilaterally absent aEEG-SEPs all four with outcome information available had a poor outcome (one was lost to follow-up): two died in the neonatal period and two developed with CP (undefined type). In all five, the aEEG background at the time of the SEP recording was either inactive (n=4) or discontinuous (n=1) and the neonatal MRI showed severe hypoxic-ischemic injury (score 2B or 3).

The one newborn with only unilaterally present aEEG-SEP but bilaterally present follow-up EEG-SEP had a favorable outcome. The aEEG during the aEEG-SEP was discontinuous and recovered to continuous trace at 52 hours postnatally. This newborn had MRI score 2A with a small perinatal infarction in the left caudate nucleus opposite side to the absent SEP.

DISCUSSION

Our data suggest that aEEG-SEPs are a practical method for evaluation of brain injury severity in asphyxiated newborns already during the first postnatal days. The classification was concordant between the aEEG-SEP and EEG-SEP in all newborns with bilaterally absent or bilaterally present responses. In accordance with previous literature [8,14], bilaterally absent responses were associated with an unfavorable outcome, and bilaterally present responses with a favorable outcome.

Theoretical basis for SEP detection using the aEEG setup

Traditionally SEPs are recorded using only a few scalp electrodes placed over the sensorimotor area at CP3 and CP4 locations [15]. Most of the previous neonatal studies also applied a similar setup [14,16–20] (some used C3 and C4 instead of CP3 and CP4). The aEEG electrodes - commonly placed at P3, P4, F3, and F4 – are, however, not located exactly over the sensorimotor area. Nevertheless, they are located anterior and posterior to the central sulcus, and bipolar montages between these electrodes should catch the tangentially oriented dipolar sources within the central sulcus; e.g. area 3b of the primary somatosensory cortex (SI), which is considered to generate the earliest cortical neonatal SEP named N1 or N20 in the literature [21–23]. Thus, routine aEEG complemented with median nerve stimulation is able catch the earliest cortical SEP components (SI response).

aEEG, EEG and SEPs in outcome prediction after perinatal asphyxia

Early outcome prediction is complicated after birth asphyxia due to the rapidly changing neurological state during recovery. A widely used additional bedside method for outcome prediction after perinatal asphyxia is continuous brain monitoring with aEEG/EEG. A normal or only mildly abnormal aEEG/EEG background during the first postnatal day is practically always associated with a favorable outcome [12,24,25]. On the contrary, a poor aEEG/EEG, including inactive, burst-suppression or very low voltage activity (corresponding to score 4 or 3 in our study), after perinatal asphyxia is only thought to be predictive of a poor outcome in hypothermia treated newborns if it fails to recover within

36-48 hours [2–6]. In our study, the four newborns with inactive aEEG still between 24 and 48 hours all had bilaterally absent aEEG-SEPs and poor outcome. Of the two with discontinuous aEEG at 24-48 hours, bilaterally absent aEEG-SEPs identified the one with poor outcome. The remaining one had unilaterally present aEEG-SEPs and bilaterally present follow-up EEG-SEP and good outcome.

There are two alternative explanations for the only one “recovering” SEP: either the SEP truly recovered between the recordings or it was not detectable in the first recording due to the technical limitations of the aEEG-SEP setup. Though this issue remains unsolved, we suggest the second option to be more likely, as in this particular case also the response detected in the EEG-SEP was best observed from the contralateral central electrode, which is absent in the aEEG-SEP montage. In a previous study, some responses that were clearly identifiable in the EEG-SEP were missed using the aEEG-montage if the number of averages i.e. the signal-to-noise ratio was simultaneously lowered [10]. Finally, as peripheral responses were not recorded with the aEEG-SEP setup, a peripheral cause of missing a cortical aEEG-SEP cannot be excluded.

Overall, our SEP results agree with previous studies in newborns under TH [8,9], by showing that bilaterally absent SEPs are an indicator for poor prognosis also during TH and already during the first two postnatal days. The only subject who had SEP initially present only in one side in aEEG-SEP recovered well. This suggests that one should interpret unilateral SEPs in HIE patients with caution, in accordance with previous studies [14].

Limitations

The present data comes from clinically indicated recordings where timing of SEP studies is somewhat variable due to logistic constraints. Hence the time delays were not fixed and we could not always perform the SEP recordings at the very early hours after birth.

The current implementation of aEEG-SEP protocol is also challenged by the lack of online averaging. Due to offline averaging, we had to record an excess number of SEP trials instead of being able to adjust length of SEP stimulation individually according to the success of SEP responses. Technical development of standard aEEG/EEG recording software would be needed to allow online averaging of evoked responses in order to build a true bedside multimodal neurophysiological brain monitoring protocol.

The relatively short clinical follow-up period may also appear as limitation. However, the main aim of the present work was to assess reliability of aEEG-SEP compared to EEG-SEP.

Future prospects

Currently, SEPs are not widely used in NICUs. Even in the institutions where neonatal SEPs are used, they are generally limited to office hours and to one time point, as they are performed by neurophysiology staff using a separate evoked potentials equipment. Combining SEPs to brain monitoring, which is widely available in the NICUs at any time with either aEEG or EEG, has the potential to overcome these time constraints in the future and to reveal the full potential of multimodal brain monitoring in the neonate. In adult intensive care, multimodal neurophysiological monitoring including EEG and

repeated SEPs has already been successfully applied to detect evolution of brain injury in comatose patients [26]. We envision that this should also be a possibility for neonates.

CONCLUSIONS

Our data show that the aEEG-SEP methodology is applicable in the challenging NICU environment. We suggest, that aEEG-SEPs are valuable in evaluation of the severity of hypoxic-ischemic brain injury after perinatal asphyxia already during the very first postnatal days, when the newborns are still under therapeutic hypothermia. Particularly, present responses predicted favorable outcome, even before recovery of sleep-wake cycling. Furthermore, bilaterally absent aEEG-SEPs from inactive or discontinuous background were always associated with an unfavorable outcome. Our results should encourage further development of clinical aEEG and EEG softwares to allow routine bedside combination of evoked potentials and aEEG/EEG, which will lead to establishing new standards for multimodal neonatal brain monitoring.

Declarations of interest: none.

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Table 1. Baseline characteristics of the study population.

Baseline characteristic	N=27
Females	13 (48%)
Received TH	25 (93%)
GA (weeks)	39,6 [1,6]
Birth weight (g)	3290 [540]
BE	-16.2 [4,9]*
pH	7,99 [0,19]
Apgar 1 min	1{1}
Apgar 5 min	3{3}
Apgar 10 min	4{1}

Data shown as n (%), mean [SD], or median {IQR}. TH = therapeutic hypothermia, GA = gestational age, EP = evoked potential, BE = base excess. *not available for two newborns. The table displays the lowest pH and BE from either umbilical, arterial or capillary sample.

Table 2. Prediction of unfavorable outcome by absent aEEG-SEPs.

	Good n=19	Poor n=4	Accuracy [%]	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]
--	0/19	4/4	100 (85–100)	100 (40–100)	100 (82–100)	100 (na.)	100 (na.)
-- or +-	1/19	4/4	96 (78–100)	100 (40–100)	95 (74–100)	80 (37–96)	100 (na.)

PPV = positive predictive value, NPV = negative predictive value

FIGURES:

Figure 1: Flow-chart of aEEG-SEP and EEG-SEP results in relation to outcome. --, SEP bilaterally absent; +-, SEP unilaterally present; ++, SEP bilaterally present; +?, SEP present unilaterally and unreliable on the other side. † = died.

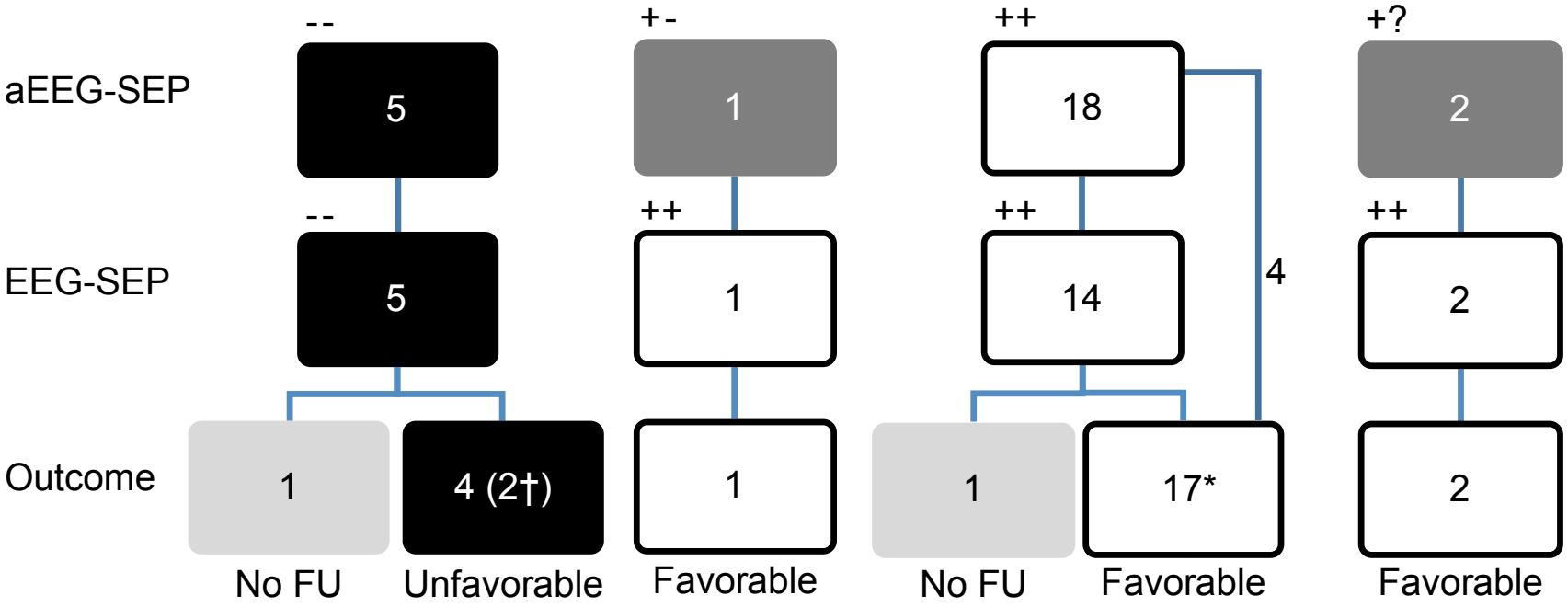

Figure 2: Relation of aEEG recovery and aEEG-SEP with outcome.

The columns show outcome, MRI finding, and hourly aEEG background scores individually for each newborn. The aEEG scores are: red = grade 4, orange = grade 3, yellow = grade 2, green = grade 1, and gray = artefact or blue = seizures (over > 50 % of the hour) preventing background scoring. F marks the timing of the full EEG-SEP if performed during the first 72 postnatal hours. --, aEEG-SEP bilaterally absent; +-, aEEG-SEP unilaterally present; ++, aEEG-SEP bilaterally present; +?, aEEG-SEP present unilaterally and unreliable on the other side; d = days; NO FU = No follow-up; CP = cerebral palsy