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Efficacy of delivery of care with Tele-continuous EEG in critically ill patients: a multicenter randomized controlled trial (Tele-cRCT study) study

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Abstract

Background Continuous electroencephalography (cEEG) has been recommended in critically ill patients although its efficacy for improving patients' functional status remains unclear. This study aimed to compare the efficacy of Tele-cEEG with Tele-routine EEG (Tele-rEEG), in terms of seizure detection rate, mortality and functional outcomes.

Methods This study is a 3-year randomized, controlled, parallel, multicenter trial, conducted in eight regional hospitals across Thailand. Eligible participants were critically ill patients aged ≥ 15 years and at-risk for developing nonconvulsive seizure (NCS)/nonconvulsive status epilepticus (NCSE). Study interventions were 24–72 h Tele-cEEG versus 30-min Tele-rEEG. Study outcomes were seizure detection rate, mortality and functional outcomes (mRS), assessed at hospital discharge, ≤ 7 days, 3-, 6-, 9-months and 1 year.

Results Two hundred and fifty-four patients were randomized, 128 and 126 patients received Tele-cEEG and Tele-rEEG, respectively. NCS/NCSE were detected more commonly in the Tele-cEEG (21.88%) than Tele-rEEG arm (14.29%) but this was not statistically significant ($p = 0.116$). Intention-to-treat, per-protocol and as-treated analysis showed non-significant differences in mortality at all assessment periods, with corresponding mortality rates of 10.03% (Tele-cEEG) versus 10.10% (Tele-rEEG) ($p = 0.894$), 9.67% versus 9.06% ($p = 0.833$) and 10.34% versus 9.06% ($p = 0.600$), respectively. Functional outcome was also not significantly different in all analyses.

Conclusions Both Tele-cEEG and Tele-rEEG are feasible, although Tele-EEG requires additional EEG specialists, budget, and computational resources. While Tele-cEEG may help detect NCS/NCSE, this study had limited power to detect its efficacy in reducing mortality or improving functional outcomes. In limited-resource settings, Tele-rEEG approximating 30 min or longer offers a feasible and potentially valuable initial screening tool for critically ill patients at-risk of seizures. However, where Tele-cEEG is readily available, it remains the recommended approach.

Trial registration Thai Clinical Trials Registry (TTCTR20181022002); Registered 22 October 2018.

Keywords Tele-continuous EEG, Critically ill patients, Randomized controlled trial, Tele-cRCT

Introduction

Continuous electroencephalography (cEEG) has been advocated as standard of care for critically ill patients at risk of occult seizures for detecting nonconvulsive seizure (NCS) and/or nonconvulsive status epilepticus (NCSE). The European Society of Intensive Care Medicine [1] and the Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society [2] recommend the use of cEEG to monitor for seizures in critically ill patients with altered mental status. This was supported by previous studies [3, 4] including a recent meta-analysis [5], which showed higher detection of seizure rate with cEEG than routine EEG (rEEG), i.e., 15.6% versus 6.3%. In addition, two large nationwide US observational studies [6, 7] reported benefits of cEEG over rEEG in lowering in-hospital mortality but at a higher cost and length of stay. However, several recent studies [8, 9] including a randomized controlled trial (RCT), failed to demonstrate any improvements in 6-month mortality with cEEG [8].

Given the contrasting findings and the challenges associated with providing cEEG in limited resource settings with its high cost and EEG specialist shortages, additional RCTs are required to evaluate any potential benefits for its use. This RCT was therefore designed to address these issues in a resource-limited setting across regional hospitals in Thailand, i.e. to assess the efficacy of Tele-cEEG relative to Tele-rEEG on seizure detection, functional outcomes and mortality at hospital discharge, ≤ 7 days, 3-, 6-, 9-, and 12-months after randomization.

Methods

This study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) 2010 checklists [10], and was listed in the Thai Clinical Trials Registry (TCTR20181022002). It was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University; Faculty of Medicine, Ramathibodi Hospital, Mahidol University; and respective local ethics committees.

Study design and setting

This RCT was a 3-year prospective, multicenter, superiority trial comparing Tele-cEEG with Tele-rEEG in patients with clinical suspicion of NCS/NCSE. A team of EEG specialists and Tele-EEG systems were established to remotely evaluate the EEG from the study hospitals, which included eight government regional hospitals across Thailand. The study protocol and patient flow were previously published [11], also see Supplemental Fig. 1.

Study outcomes

The primary outcomes were seizure detection, functional outcomes, and mortality measured at hospital

discharge, ≤7 days, 3-, 6-, 9-months and 1 year after randomization. The secondary outcomes were described in the published protocol [11].

Screening and randomization

A dedicated nurse or neurologist screened participants against the eligibility criteria: (1) aged ≥15 years; (2) suffering from at least one of the 5 conditions i.e., (2.1) recent clinical seizure/status epilepticus without return to baseline; (2.2) severely depressed consciousness from any cause; (2.3) intracranial hemorrhages with any of traumatic brain injury (TBI) and Glasgow Coma Scale (GCS) 6–12 [12] or subarachnoid hemorrhage (SAH) with Hunt & Hess Classification grade ≤IV or GCS >5 [13] or intracerebral hemorrhage (ICH) with ICH score ≤3 [14]; (2.4) suspected NCS/NCSE in patients with altered mental status, cause indeterminate; and (2.5) central nervous system (CNS) infection with altered mental status; (3) their relatives were willing to provide signed-informed consent; and (4) caregivers were able to provide functional outcome data after discharge. We excluded patients with the following conditions: post cardiac arrest, cancer stage IV, acquired immunodeficiency syndrome with CD4 count <200 cells/mm^3 or with opportunistic infections, alcoholic intoxication with/without delirium tremens, poor functional outcome at pre-admission state i.e., modified Rankin Scale (mRS) 4–6, and extensive lacerations, skin lesions, or surgical wound preventing electrode placement. Web-based screening and central block randomization were as detailed in the published protocol [11].

Blinding

Participants or caregivers were unblinded due to the nature of the assigned EEG interventions. However, dedicated outcome assessors were blinded to patient allocation.

Intervention

Both EEG types used 23 electrodes placed according to the International 10–20 system and were recorded with video.

Tele-EEG system

A standardized portable video-EEG system was used comprising reusable electrodes, a headbox, amplifiers, and a mobile computer with video recording capabilities. A portable Wi-Fi router facilitated internet connectivity. Decentralized systems were used to provide continuous remote access for EEG specialists for constant monitoring using licensed TeamViewer® software. EEG data were uploaded to cloud storage (offline) with daily downloads to a bespoke, secure EEG database server at Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) which enabled further off-line review of questionable EEG findings, Fig. 1. This secure decentralized system allowed specialists to access EEGs anytime, anywhere, with findings reported via a web-based case record form. EEG specialists typically discussed findings with treating neurologists before determining patient management.

Conducting Tele-EEG

EEG recordings were initiated within 24 h after randomization, during working days, weekends and bank holidays, with the application of electrodes by an EEG technician between 8 am and 4 pm with notification of the on-call specialist to prepare for EEG review.

Tele-cEEG EEG findings were reported every 2, 6, or 12 h depending on clinical urgency, as determined by clinical data, prior seizure frequency and the initial 30-min EEG findings. EEG was monitored for at least 24 h and was continued until 72 h if seizures were detected. However, if seizures were still present at 72 h, the Tele-cEEG could be continued and then discontinued after seizure cessation for 12 h. Continuing Tele-cEEG monitoring after 72 h was treated as co-intervention.

Tele-rEEG EEG was monitored for 30 min and interpreted by a specialist with results reported to the local neurologist within 2 h. Patients could be switched to Tele-cEEG or Tele-rEEG repeated if the initial findings suggested seizures, epileptiform activity, or periodic discharges [15]. In this case, the Tele-cEEG was treated as a co-intervention and adjusted in the analysis.

Standard consensus protocols for investigation and management of status epilepticus [16] were followed for all patients.

EEG reviewing organization

The seven EEG specialists included in this trial were all certified epileptologists with training in either Thailand and/or North America (US and Canada). Each on-call duration lasted for 24 h.

The terminology and definition of the EEG wave forms used were based on the American Clinical Neurophysiology Society 2012 version [17]. We defined NCSE according to the Salzburg criteria [18]. A unified EEG report form was created as part of web-based CRF.

Sample size calculation

Based on the most relevant study by Khawaja et al. [9], the proportion of general patients with poor outcomes (mRS 3–6) was used, which was estimated at 0.829. To detect a clinically meaningful difference in poor

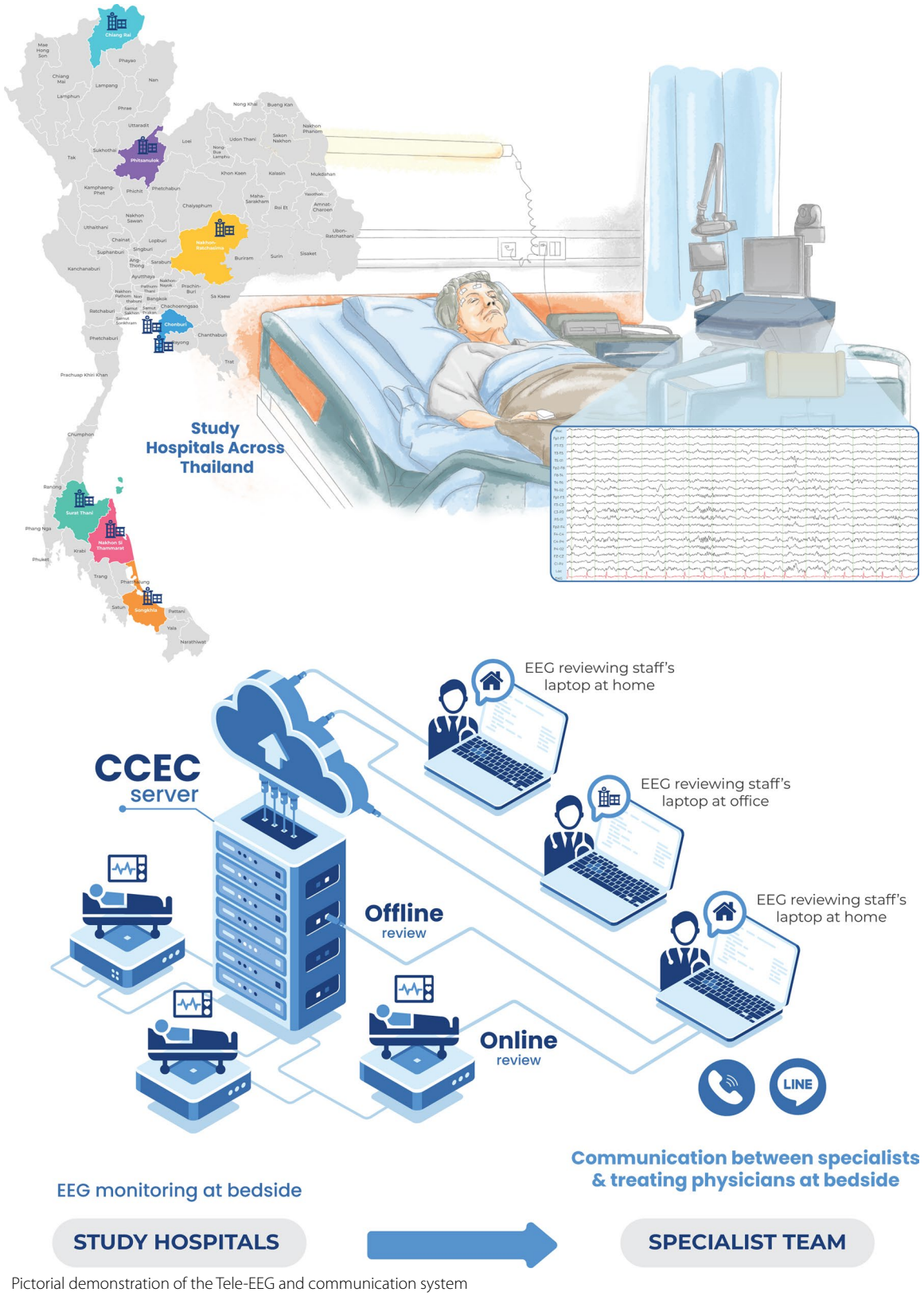


Fig. 1 Pictorial demonstration of the Tele-EEG and communication system

functional outcome of 0.1, with a ratio of intervention versus control of 1:1, and type I and II errors of 0.05, and 0.2, the required sample size was 270 per arm, requiring a total of 648 participants, assuming a 20% loss to follow up.

Data collection and management

Nineteen CRFs were paper-based, except for the web-based screening and EEG reporting forms (https://www3.ra.mahidol.ac.th/CEB/TeleEEG/login.php); all were completed by outcome assessors (i.e., nurses or local-neurologist) [11]. Data audits were performed every 1–2 months during the first 6 months and then every 3 months. A Data and Safety Monitoring Board evaluated data accuracy and patient safety throughout the study period.

Statistical analysis

All analyses were performed using STATA 18.0. Seizure detection rate was compared between Tele-cEEG and Tele-rEEG groups using Chi-square test. Intention-to-treat (ITT), per-protocol (PPA) and as-treated analyses (ATA) were applied for functional outcomes and mortality. For functional scores, two outcomes were considered: (1) changes of functional score post hospital discharge from favorable (mRS 0–3) to poor outcome (mRS 4–5) and vice versa and (2) the actual functional scores assessed at ≤ 7 days, 3-, 6-, 9-, and 12-months post recruitment. A competing risk model with sub-distribution hazard was applied considering death as a competing event. Sub-distribution HR (SHR) along with 95% CI were estimated accordingly. A mixed-effect linear regression was applied by fitting continuous mRS scores against intervention groups and time to assess within-group changes (ΔmRS) and compare scores between intervention arms at each time point. For mortality, survival analysis and Cox proportional-hazards models were used to estimate mortality rate and treatment effects using hazard ratios (HR). Adjusted models included switching intervention arm post randomization, presence of NCS/NCSE, refractory status epilepticus (RSE), antiseizure medication (ASM) prescribed after randomization, and immunomodulation therapy (IMT).

A pre-specified subgroup analysis was performed including age group, severity scores at baseline, i.e., Acute Physiology and Chronic Health Evaluation IV, Simplified Acute Physiology Score II, GCS and Full Outline of UnResponsiveness Score, and indication for enrolment.

Results

Baseline characteristics

The patients were recruited from Jan 2, 2020, to Jun 15, 2022. Patient enrolment was significantly impacted by the Covid-19 pandemic and was reported to the Ethics Committee. Only 310 patients were screened, 56 were excluded based on the inclusion/exclusion criteria, leaving 254 recruited patients for randomization, Fig. 2. Of these, 128 and 126 patients were randomly assigned to receive Tele-cEEG and Tele-rEEG, respectively. All patients received their randomly allocated interventions. Baseline characteristics between both interventions were comparable (Table 1), but some treatment factors were significantly different i.e., ASM and/or anesthetic agent ($p = 0.005$) and IMT post randomization ($p = 0.032$), Supplemental Table 1.

Outcomes

Four patients in each arm were lost to follow-up after hospital discharge (see the CONSORT diagram). All patients (128 vs 126) who were randomized to receive interventions were included for ITT. Eight patients in the Tele-cEEG arm received EEG monitoring > 72 h, and 43 patients in Tele-rEEG arm crossed over to Tele-cEEG as their initial 30-min EEG findings showed seizures, epileptiform activity, or periodic discharges. As a result, 120 versus 83, and 163 versus 83 patients were included for PPA and ATA, respectively.

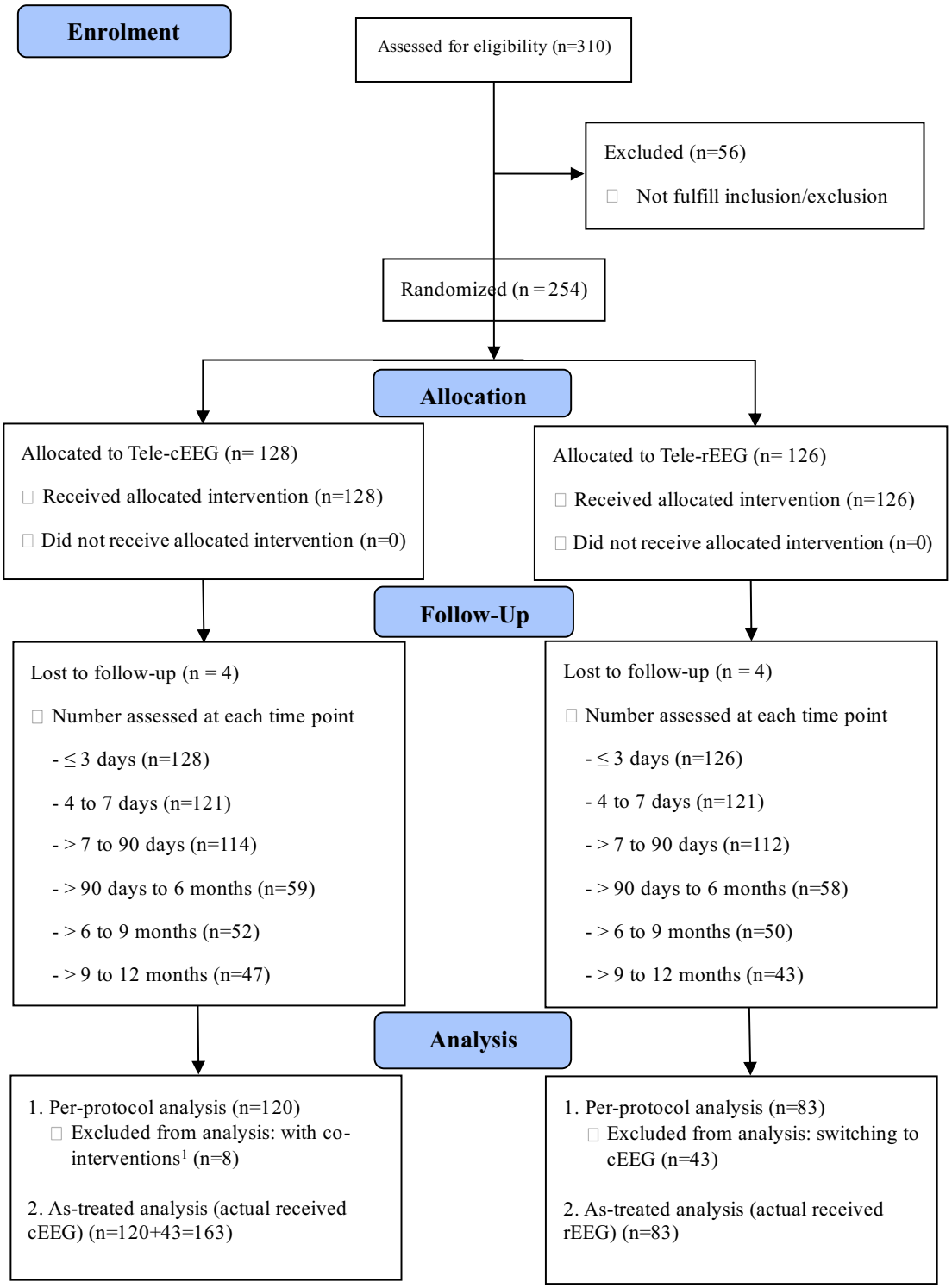
Seizure detection rate

The inter-rater agreement for the interpretation of EEG patterns was reported in the protocol [11]. Overall, Tele-EEG detected NCS/NCSE in 46 (18.11%) of the 254 patients. A higher detection rate was noted in Tele-cEEG than Tele-rEEG, 28 (21.88%) versus 18 (14.29%), but this was not significant ($p = 0.116$), Supplemental Table 2. Different detection rates were observed for NCS (i.e., 14.06% vs 7.94%), and lower for NCSE (i.e., 12.50% vs 10.32%).

Functional outcome

Functional changes after hospital discharge and cumulative incidence were assessed. A mixed-effect ITT analysis was applied by regressing mRS on interventions and time; overall mean mRS score did not differ significantly between Tele-cEEG and Tele-rEEG with mean mRS of 4.08 (3.80, 4.37) vs 4.10 (3.81, 4.39) respectively, $p = 0.942$, Table 2 and Supplemental Fig. 2; change in mRS scores (ΔmRS) from baseline improved over time for both interventions, Table 2, however these did not differ significantly between both arms at each time point. PPA and ATA analyses also failed to identify any significant differences in functional outcomes between both arms, Supplemental Tables 3, 4 and Supplemental Figs. 3, 4.

Subgroup analysis by baseline functional mRS score was performed by applying a competing risk analysis indicating a trend towards less worsening (from mRS 0–3 → 4–5) for Tele-cEEG than Tele-rEEG, but this was



[1] co-intervention = continued monitoring > 72 h

Fig. 2 CONSORT diagram

Table 1 Baseline characteristics

Patient factors	Tele-cEEG (n = 128)	Tele-rEEG (n = 126)
Age (years), mean (SD)	54.45 (18.56)	54.08 (19.26)
Male gender, n (%)	69 (53.91)	75 (59.52)
Comorbidity, n (%)		
Diabetes mellitus	36 (28.12)	35 (27.78)
Liver disease	10 (7.81)	11 (8.73)
Malignancy	2 (1.56)	3 (2.38)
HIV	3 (2.34)	1 (0.79)
CKD	20 (15.62)	18 (14.29)
CHF	3 (2.34)	2 (1.59)
MI	8 (6.25)	4 (3.17)
COPD	2 (1.56)	2 (1.59)
PVD	2 (1.56)	0 (0.00)
CVA or TIA	16 (12.50)	12 (9.52)
Dementia	2 (1.56)	0 (0.00)
Hemiplegia	7 (5.47)	5 (3.97)
Connective tissue diseases	3 (2.34)	5 (3.97)
Peptic ulcer diseases	2 (1.56)	2 (1.59)
CCI, median (IQR)	2.0 (1.0, 5.0)	2.0 (0.0, 4.0)
GCS, median (IQR)	6.0 (3.0, 8.0)	6.0 (3.0, 8.0)
FOUR, median (IQR)	7.0 (4.0, 9.5)	7.0 (4.0, 9.0)
SAPS II, mean (SD)	50.87 (15.97)	51.40 (16.70)
APACHE IV, mean (SD)	68.29 (26.70)	67.47 (27.16)
Clinical seizure/SE, n (%)		
Presence[a]	90 (70.31)	87 (69.05)
Absence	38 (29.69)	39 (30.95)
Place where clinical SE occurred, n (%)		
In-hospital SE	40 (68.97)	33 (71.74)
Out-of-hospital SE	18 (31.03)	13 (28.26)
Refractory SE, n (%)		
Yes	34 (58.62)	18 (40.91)
No	24 (41.38)	26 (59.09)
STESS, mean (SD)	3.67 (1.40)	3.47 (1.21)
EMSE, median (IQR)	39.0 (22.0, 62.0)	33.0 (26.5, 58.5)

Tele-cEEG, Tele-continuous EEG; Tele-rEEG, Tele-routine EEG; SD, Standard deviation; DM, Diabetes millitus; HIV, Human immunodeficiency virus; CKD, Chronic kidney disease; CHF, Congestive heart failure; MI, Myocardial infarction; COPD, Chronic obstructive pulmonary disease; PVD, Peripheral vascular disease; CVA, Cerebrovascular accident; TIA, Transient ischemic attack; CCI, Charlson comorbidity index; IQR, Interquartile range; GCS, Glasgow Coma Scale; FOUR, Full Outline of UnResponsiveness; SAPS II, Simplified Acute Physiology Score; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; CS, Convulsive seizure; CSE, Convulsive status epilepticus; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology-based Mortality Score in Status Epilepticus

[a] Not including seizures after randomization

not significant with SHR 0.44 (0.04, 4.73); $p = 0.502$. Likewise, both groups tended to have similar functional improvement (from mRS 4–5 → 0–3) after discharge, with SHR of 1.01 (0.56, 1.84); $p = 0.962$, Supplemental Fig. 5 and Supplemental Table 5.

Mortality outcome

ITT did not reveal a treatment effect for Tele-cEEG relative to Tele-rEEG in reducing mortality rates, with $_{\text{unadjusted}}$HR (95%CI) of 0.98 (0.72, 1.34; $p = 0.895$). After adjustment for potential confounders (i.e., switching intervention, presence of NCS/NCSE, antiseizure medication after randomization, RSE, and IMT), the ITT analysis remained non-significant with similar survival curves observed (Supplemental Fig. 6) and an $_{\text{adjusted}}$HR of 0.93 (0.66, 1.29; $p = 0.652$), see Table 3. Of the potential confounders assessed, receiving IMT was associated with significantly reduced mortality, with $_{\text{adjusted}}$HR of 0.43 (0.20, 0.94; $p = 0.035$). Neither PPA nor ATA demonstrated significant treatment

Table 2 Comparison of mRS scores after receiving interventions: a mixed-effect model with intention-to-treat analysis

Outcomes	Tele-cEEG (n = 128)	Tele-rEEG (n = 126)	Difference coefficient (95% CI)	*p* value
Overall mean mRS score over time (95% CI)	4.08 (3.80, 4.37)	4.10 (3.81, 4.39)	−0.02 (−0.43, 0.40)	0.942
Mean score at each time point (95% CI)				
≤ 7 days	4.65 (4.37, 4.94)	4.73 (4.44, 5.02)	−0.07 (−0.48, 0.33)	0.719
> 7 to 90 days	4.45 (4.12, 4.77)	4.42 (4.08, 4.76)	0.03 (−0.44, 0.49)	0.909
> 90 days to 6 months	3.47 (3.11, 3.82)	3.44 (3.08, 3.80)	0.03 (−0.48, 0.53)	0.922
> 6 to 9 months	2.67 (2.27, 3.07)	3.04 (2.64, 3.45)	−0.37 (−0.94, 0.20)	0.202
> 9 to 12 months	2.52 (2.17, 2.87)	2.50 (2.14, 2.86)	0.02 (−0.48, 0.52)	0.946
	Within-group change of mRS score (Δ mRS) from baseline i.e., duration of ≤ 7 days after randomization coefficient (95% CI); *p* value		Between-group comparison of change of mRS (Δ mRS) from baseline	
			Difference coefficient (95% CI)	*p* value
> 7 to 90 days	−0.21 (−0.51, 0.09); 0.178	−0.31 (−0.63, 0.01); 0.058	0.10 (−0.34, 0.54)	0.651
> 90 days to 6 months	−1.19 (−1.52, −0.86); < 0.001*	−1.29 (−1.62, −0.95); < 0.001*	0.10 (−0.37, 0.57)	0.678
> 6 to 9 months	−1.98 (−2.36, −1.60); < 0.001*	−1.69 (−2.07, −1.30); < 0.001*	−0.30 (−0.84, 0.24)	0.281
> 9 to 12 months	−2.14 (−2.46, −1.81); < 0.001*	−2.23 (−2.57, −1.89); < 0.001*	0.09 (−0.38, 0.56)	0.703

mRS, Modified Rankin Scale; CI, Confidence interval

*$p < 0.05$ indicates statistical significance

Table 3 Estimation of mortality rates after receiving intervention and treatment effect by intention-to-treat analysis

Intervention	Person-month	Number of deaths	Incidence/100/month	Median survival time (months)	*p* value	$_{unadjusted}$HR[a]	95% CI	*p* value
Tele-cEEG (n = 128)	777.93	78	10.03	3.34	0.894	0.98	0.72, 1.34	0.895
Tele-rEEG (n = 126)	772.25	78	10.1	3.48				
Adjusting for switching arm, presence of NCS/NCSE, RSE and treatment factors[b]						$_{adjusted}$HR[a]	95% CI	*p* value
Tele-cEEG (n = 128)						0.93	0.66, 1.29	0.652
Tele-rEEG (n = 126)								
Effects of covariates on mortality in the final model[c]						$_{adjusted}$HR[a]	95% CI	*p* value
Switching to receive Tele-cEEG in Tele-rEEG arm after randomization, as compared with no switching						1.63	0.73, 3.65	0.234
Presence of NCS/NCSE						1.10	0.67, 1.79	0.706
RSE						1.32	0.78, 2.21	0.302
Antiseizure medication prescribed after randomization						1.02	0.67, 1.54	0.943
Immunomodulation therapy (IMT)						0.43	0.20, 0.94	0.035*

HR, Hazard ratio; RSE, Refractory status epilepticus

[a] Tele-cEEG relative to Tele-rEEG

[b] Treatment factors after randomization included ASMs prescribed after randomization and immunomodulation therapy

[c] Final model included assigned intervention (Tele-cEEG vs Tele-rEEG), switching intervention arm after randomization, presence of NCS/NCSE, RSE, antiseizure medication prescribed after randomization and immunomodulation therapy

*$p < 0.05$ indicates statistical significance

effects with corresponding $_{unadjusted}$HR of 1.04 (0.72, 1.49; $p = 0.834$) and 1.10 (0.78, 1.54; $p = 0.599$). After adjustment, the corresponding survival probabilities remained non-significant with $_{adjusted}$HRs of 1.06 (0.72, 1.57; $p = 0.764$) and 1.10 (0.77, 1.59; $p = 0.603$), respectively, Supplemental Tables 6, 7 and Supplemental Figs. 7, 8.

Pre-specified subgroup analysis

This was performed to identify patient characteristics (i.e., age, patient's condition) that may have benefitted from the Tele-cEEG intervention. A lower death rate was noted for patients with intracranial hemorrhages screened with Tele-cEEG i.e., 2.41% versus 32.04% ($p = 0.020$), but this was not significant in the adjusted

model (HR = 0.74 [95% CI 0.34, 1.58]; $p = 0.433$). A higher death rate was observed among Tele-cEEG patients with CNS infection, 10.44% versus 4.22% ($p = 0.025$), Supplemental Table 8.

Discussion

We performed an RCT including 128 and 126 patients in Tele-cEEG and Tele-rEEG arms respectively. Functional scores within 1-year for both interventions were similar (i.e., mRS 4.08 vs 4.10). Tele-cEEG tended towards less worsening (from mRS 0–3 → 4–5), although this was not significant. Receiving Tele-cEEG did not lead to reduced mortality within 1-year compared to Tele-rEEG. NCS/NCSE detection rate was higher in the Tele-cEEG arm compared to the Tele-rEEG arm (21.88% vs 14.29%) but this was not significant, in part constrained by insufficient study power. Tele-cEEG was associated with a significantly lower death rate in patients with intracranial hemorrhages compared to the Tele-rEEG arm, but a concomitant higher death rate in patients with CNS infections; both estimates were considered imprecise and reliant on verification by independent replication.

Although cEEG recording is recommended in critical care patients for the detection of NCS/NCSE, its routine clinical use remains limited due to costs and specialist shortages. Short EEG (i.e., rEEG) is more affordable, but has lower sensitivity to detect NCS/NCSE [5] which may result in undertreatment and poorer outcomes. In the current era of telemedicine, Tele-EEG was designed to assist local neurologists for remote evaluation of EEG interpretation and guidance on appropriate treatment management. We established a Tele-EEG system for the purpose of assessing the efficacy of Tele-cEEG and Tele-rEEG in a limited resource setting, and have provided evidence that both are feasible in clinical practice, but dependent on EEG specialists, sufficient budget and dedicated computational infrastructure. This is the second RCT assessing the prognostic impact of cEEG compared to rEEG. The first, CERTA [8], used a shorter outcome assessment at 6 months and also did not find a superior effect of cEEG over rEEG; the authors suggested that rEEG may be an alternative to cEEG in limited-resource settings.

Seizure detection rate

Recent systemic review and meta-analysis showed higher detection of NCS/NCSE with cEEG compared to rEEG in patients with a mixed cause of admission [5], similar to our findings. In addition, the detection rate for both cEEG and rEEG was higher in our study compared to the CERTA RCT [8] (i.e., 15.7% vs 4.4%), which may have been due to variation in the study populations recruited. CERTA recruited critically ill patients with impaired consciousness and no recent seizure in contrast to our study which included all patients at risk of developing NCS/NCSE, with or without recent seizures according to the 2012 Neurocritical Care Society guidelines [19]. NCS/NCSE detection is likely greater in our study due to the higher risk population, in whom NCS/NCSE may be quickly detectable, even after a short monitoring period.

Mortality and functional outcomes

Two large US observational nationwide studies in adults showed favorable use of cEEG over rEEG where cEEG was associated with lower in-hospital mortality [6, 7]. Khawaja et al. showed no benefits of cEEG on functional outcomes, with no differences in mortality rates compared to no EEG, but cEEG was associated with longer hospitalization and more frequent modifications of ASMs [9]. The CERTA study [8] showed that at 6-month follow-up assessment, cEEG was associated with increased seizure detection and modification of ASM but not with improved outcome compared to repeated rEEGs. Our Tele-cRCT study which compared cEEG and rEEG in a different patient cohort (i.e., increased risk of seizures and longer assessment periods up to 12 months) also found similar effects on mortality and functional outcomes. Our findings also provide evidence of IMT benefit in critical care patients but this requires further confirmation and independent validation [20–22].

Patients subgroups that may benefit from cEEG

Patients with intracranial hemorrhages including TBI, SAH and ICH may benefit more from Tele-cEEG rather than Tele-rEEG given the lower death rate of 2.41% vs 32.04%. Based on our previous meta-analysis, cEEG helps detect NCS/NCSE which occurs in 10–13% of this population [5]. Lower detection rates by Tele-rEEG may lead to under reporting of ongoing seizures leading to prolonged ICU admissions and poorer longer-term outcomes [23–29]. A previous study in the ICH population i.e., the PEACH trial [30], investigated the effect of levetiracetam (LEV) on seizure risk in ICH patients, using continuous EEG monitoring for 48 h within 24 h of enrollment. The PEACH trial reported an overall mortality of 18% (9/50), although a more accurate mortality analysis based on adequate EEG recordings showed 15.79% mortality (3/19) in the LEV arm and 26.09% (6/23) in the placebo arm. This is higher than the 2.41% mortality observed in our Tele-cEEG intracranial hemorrhage subgroup. This discrepancy likely reflects differences in patient populations; our study included only lower-risk patients (TBI with GCS 6–12, SAH with Hunt and Hess ≤ IV or GCS > 5, ICH with ICH score ≤ 3), whereas the PEACH trial likely included patients at higher risk.

Regarding the higher death rate observed among Tele-cEEG patients with CNS infection in our study population. Low risk of mortality in status epilepticus patients due to CNS infection was supported by a recent study [31]. CNS infection is a treatable condition if addressed promptly [32–34]. Higher levels of CNS infections were noted in the Tele-rEEG (n = 35, 56.5%) arm compared to the Tele-cEEG (n = 27, 43.5%) arm, which may account for the lower death rates observed. A caveat of these subgroup analyses is obviously the small sample sizes; nevertheless, we provide the results as these were specified a priori [11].

Clinical implications

To date, given the lack of clear benefits of cEEG over rEEG in reducing either mortality or improving functional outcomes in both ours and the previous RCT [8], Tele-rEEG represents a pragmatic approach, especially in resource-limited settings. Our findings support an initial screen with Tele-rEEG in all patients at risk of seizures, then individual consideration of whether to continue with Tele-cEEG based on initial EEG findings i.e., presence of epileptiform discharges and/or seizures or applying 2HELPS2B model to aid clinical judgement [35].

Limitations

Our study had several limitations. First, we were unable to achieve the proposed sample size due to public health restrictions in response to the Covid-19 pandemic at the time of recruitment, resulting in a final sample size smaller than originally planned and a reduced study power of 0.485 (compared to the planned 0.80). This increased the risk of a type II error. Second, approximately one-third of patients at high risk of seizures in the Tele-rEEG arm crossed over to receive Tele-cEEG, impacting study randomization and potentially biasing our findings towards the null. However, it was considered unethical not to provide further EEG monitoring in these patients. Third, the subgroup analysis was restricted by the small number of patients specific to each subgroup which resulted in less precisely estimated intervention effects. Further studies in larger sample sizes would be required to replicate our findings. Forth, time from seizure detection to treatment initiation and the time to seizure cessation were not systematically collected.

Conclusion

This study demonstrates the feasibility of both Tele-cEEG and Tele-rEEG in critical care, although implementation of the former requires specialized expertise, adequate infrastructure, and resources. While both modalities may improve functional outcomes in critically ill patients, and Tele-cEEG may aid in detecting NCS/NCSE, our study lacked sufficient power to definitively demonstrate superiority of Tele-cEEG over Tele-rEEG in reducing mortality or improving functional outcomes across diverse pathologies. Although trends toward comparable efficacy were observed, larger studies focusing on more homogeneous patient subgroups are needed. Tele-rEEG offers a potentially valuable alternative to Tele-cEEG in resource-constrained settings, particularly for patients at risk of seizures; however, Tele-cEEG remains the recommended treatment option when readily available.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05246-x.

Additional file1 (TIF 37691 KB)
Additional file2 (TIF 3881 KB)
Additional file3 (TIF 3881 KB)
Additional file4 (TIF 3881 KB)
Additional file5 (TIF 3829 KB)
Additional file6 (TIF 3881 KB)
Additional file7 (TIF 3881 KB)
Additional file8 (TIF 3881 KB)
Additional file9 (DOCX 40 KB)

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Chusak Limotai had full access to all of the study data and takes responsibility for data integrity and accuracy of the data analysis and contributed to study concept and design, data acquisition and analysis, drafting the manuscript, critical revision of the manuscript for important intellectual content, statistical

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Availability of data and materials
All data relevant to the study are included in the article or uploaded as supplementary information. Data generated by our research to supports our manuscript will be made available upon reasonable request, where legally and ethically possible.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (IRB No.627/61); Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA 2019/723); and all local ethics committee of the study hospitals. Every participant or their relatives or caregivers provided signed-informed consent.

Competing interests
None of the authors have associations with any commercial entities that provided support for the work reported in this manuscript. None of the authors have associations with commercial entities that could be viewed as having an interest in the general area of the manuscript. None of the authors have any similar financial associations involving their spouse or children under 18 years of age. None of the authors have non-financial associations that may be relevant to the manuscript.

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