Quantitative burst suppression on serial intermittent EEG in refractory status epilepticus

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ABSTRACT

Objectives: In refractory status epilepticus (RSE), the optimal degree of suppression (EEG burst suppression or merely suppressing seizures) remains unknown. Many centers lacking continuous EEG must default to serial intermittent recordings where uncertainty from lack of data may prompt more aggressive suppression. In this study, we sought to determine whether the quantitative burst suppression ratio (QBSR) from serial intermittent EEG recording is associated with RSE patient outcome.

Methods: We screened the EEG database to identify non-anoxic adult RSE patients for EEG and chart review. QBSR was calculated per 10-second EEG epoch as the percentage of time during which EEG amplitude was <3 mV. Patients who survived 1–3 months after discharge from ICU and hospital comprised the favorable group. Further to initial unadjusted univariate analysis of all pooled QBSR, we conducted multivariate analyses to account for individual patient confounders ("per-capita analysis"), uneven number of EEG recordings ("per-session analysis"), and uneven number of epochs ("per-epoch analysis"). We analyzed gender, anesthetic number, and adjusted status epilepticus severity score (aSTESS) as confounders.

Results: In 135,765 QBSR values over 160 EEG recordings (median 2.17 h every 24 h) from 17 patients on Propofol, Midazolam, and/or Ketamine, QBSR was deeper in the favorable group (p < 0.001) on initial unadjusted analysis. However, on adjusted multivariate analysis, there was consistently no association between QBSR and outcome. Higher aSTESS consistently associated with unfavorable outcome on per-capita (p = 0.033), per-session (p = 0.048) and per-epoch (p < 0.001) analyses. Greater maximal number of non-barbiturate anesthetic associated with favorable outcome on per-epoch analysis (p < 0.001).

Conclusions: There was no association between depth of EEG suppression using non-barbiturate anesthetic and RSE patient outcome based on QBSR from serial intermittent EEG. A per-epoch association between non-barbiturate anesthetic and favorable outcome suggests an effect from non-suppressive time-varying EEG content.

Significance: Targeting and following deeper burst suppression through non-barbiturate anesthetics on serial intermittent EEG monitoring of RSE is of limited utility.

1. Introduction

Status epilepticus (SE) is a common neurological emergency, defined by either a failure of mechanisms responsible for seizure termination, or initiation of mechanisms responsible for an abnormally prolonged seizure (Trinka et al., 2015). Defined as failing a 1st line benzodiazepine and 2nd line non-benzodiazepine anti-seizure medication (ASM), refractory status epilepticus (RSE) develops in up to 43% of SE patients (Cooper et al., 2009; Drislane et al., 2009; Novy et al., 2010; Sutter et al., 2013; Kantanen et al., 2015). Current guidelines recommend using 3rd line intravenous anesthetic therapy (IVAT) to obtain variable EEG targets, including burst suppression (BS), or seizure suppression defined as absence of seizures but not necessarily EEG suppression (Meierkord et al., 2010; Brophy et al., 2012).

While most recent studies assessing the optimal degree of BS have used continuous EEG (cEEG) (Claassen et al., 2002; Rossetti and Lowenstein, 2011; Johnson et al., 2016; Phabphal et al., 2018), many centers lack access and must default to serial intermittent EEG (siEEG) in SE management (Zehtabchi et al., 2020). While diagnostic clarification could be achieved in 96% of neurosurgical patients with clinical suspicion of nonconvulsive SE using...
The initial 30 min of EEG (Krøigård et al., 2019), intermittent EEG may fail to detect seizures which follow circadian cycles (Baud et al., 2021). The resultant uncertainty about intermittent recordings may bias IVAT toward BS to minimize the chance of seizure recurrence when there are literally no data. However, IVAT is associated with mechanical ventilation, hypotension, prolonged immobilization, cardiovascular complications, and other adverse effects (Claassen et al., 2002; Rossetti et al., 2011). With quantitative EEG (QEEG), there is opportunity to generate high data volume on EEG suppression, such as the quantitative burst suppression ratio (QBSR), to capture the full richness of longitudinal data available over even intermittent sessions. Accordingly, we aimed to assess whether QBSR from siEEG is associated with morbidity and mortality in RSE.

2. Methods

This study was approved by the institutional Research Ethics Board. We screened the EEG database at the Winnipeg Health Sciences Center between February 2017 and May 2018 to identify RSE patients for EEG and chart review. EEG was acquired using the 10–20 system (Natus, Oakville, ON, Canada), sampled at 500 Hz, and available every day for up to 16 h, which resulted in siEEG recording sessions. To calculate QBSR, Persyst 12 QEEG software (Prescott, USA) first divides EEG data per hemisphere into 10 s epochs. The Persyst suppression ratio is defined as the percentage of a 10 s epoch during which no EEG activity exceeds 3 µV in 0.5 s steps. Persyst 12 then smoothes suppression ratios as part of a 60-second running average (Elmer et al., 2016). The QBSR is finally calculated as the average smoothed suppression ratio per 10-second epoch between hemispheres.

2.1. General decision algorithm

At our institution, any clinician can order a screening EEG to rule out nonconvulsive status epilepticus (NCSE) for unexplained decreased level of consciousness (LOC) or after the convulsive phase of a generalized tonic-clonic seizure. NCSE was defined by the Salzburg criteria (Leitinger et al., 2015). If NCSE was detected and seizures were refractory to the point of requiring 3rd line IVAT (i.e. RSE), then EEG recording stopped for patient transfer to the medical or surgical intensive care unit (ICU). In the ICU, EEG is typically reordered on a daily basis in a serial intermittent (siEEG) fashion to assess whether IVAT can be decreased or discontinued based on the degree of seizure suppression or BS. At the start of siEEG recording, the ICU team usually weaned IVAT unless there was already ongoing NCSE. After weaning, the ICU team usually resumed IVAT if NCSE recurred, or if more ictal-appearing EEG patterns along the interictal-ictal continuum (IIC) emerged. This is because cEEG was not available to ensure that these IIC patterns did not evolve into NCSE. If IVAT was resumed, then the EEG was titrated to either seizure suppression or BS. Occasionally, IVAT was also used for intubation before administering 2nd line ASM due to decreased LOC from either the 1st line benzodiazepine or SE itself. IVAT may have also been used to sedate patients for other reasons (e.g. agitation, intracranial pressure control).

2.2. Patient and EEG selection

Inclusion criteria were siEEG in RSE patients over age 18 years. Exclusion criteria were (1) anoxic brain injury, and (2) RSE recurrence in the same admission, or over different admissions within the review period. Recurrent RSE was excluded to avoid additional confounding because predictors and outcomes in recurrent RSE can differ from the first RSE episode (Rossetti, 2015). We reviewed charts for survival, functional status, gender, maximal number of IVAT encountered per patient (“IVAT number”), age, history of previous seizures, level of consciousness (LOC) at seizure onset, and worst seizure type at onset to calculate the “Status Epilepticus Severity Score” (STESS) (Rossetti et al., 2008). Outcome was dichotomized into favorable and unfavorable groups based on discharge from hospital, and survival to 1 or 3 months. From 24 RSE patients, we excluded 3 patients due to anoxic brain injury, 3 patients due to RSE recurrence (in the same or different admissions within the review period), and 1 patient due to no evidence of RSE on EEG following empiric IVAT. Sufficient data were available to compare the number of IVAT at the start of recording to the number of IVAT at the end of recording in 139 siEEG records from the 17 included patients. In 37% of recordings, the number of IVAT at the end of recording was lower than the number of IVAT at the start of recording. In 23% of recordings, the number of IVAT at the end of recording was higher than the number of IVAT at the start of recording. There was no net IVAT change in 40%.

2.3. Statistics

Univariate analyses used Wilcoxon rank sum testing, except for gender which used the chi-squared test. To assess reproducibility of relation between QBSR and patient outcome, we conducted 3 stratified multivariate analyses: collapsing QBSR to one measure per patient (“per-capita analysis”), per EEG recording (“per-session analysis”), or “un-collapsed” (“per-epoch analysis”). We treated STESS, gender, and IVAT number as confounders. In per-capita analysis, we conducted multivariate logistic regression of median patient QBSR against outcome. In per-session analysis, we used a generalized estimating equation (GEE) marginal model (assuming an autocorrelative structure) to account for uneven numbers of EEG sessions between patients. In per-epoch analysis, we again assumed an autocorrelative structure to conduct quasi-least squares regression (QLS) to account for uneven numbers of repeated QBSR measures between patients. All analyses were performed using Stata 14 (Statacorp, College Station, USA), except that QLS was conducted using the ‘geepack’ package in MATLAB (Natick, USA).

3. Results

3.1. Patient characteristics

7/17 patients comprised the favorable group. 15 patients presented in NCSE, which followed bilateral tonic-clonic seizures in 5 patients, focal seizures in 3 patients, and myoclonic seizures in 2 patients (Table 1). The overall resultant mortality rate was 58.8%. All patients discharged from hospital survived ≥1 month after RSE resolved. Where data were available, all surviving 1 month also survived 3 months. RSE etiology was heterogeneous. Median age of all 17 patients was 63 years with the favorable group significantly younger (median 58 vs. 72 years, p = 0.0357, Table 1). Due to poor documentation on LOC before intubation, we were forced to exclude LOC to calculate an adjusted STESS (aSTESS) scored out of 5 instead of 6 points. Median aSTESS for all patients was 3 with the favorable group trending to less severely ill (median 3 vs. 5, p = 0.0658). Median RSE duration was 5 days with no difference between groups (median favorable 5 vs. unfavorable 7, p = 0.73). Propofol, midazolam and ketamine IVAT were used individually or in combination. Median IVAT number for all patients was 2 with no difference between groups (median 2 vs. 2, p = 0.83). 9/17 patients were male with no difference between groups (favorable 4 vs. unfavorable 5, p = 0.77).
Table 1
Patient characteristics, duration/cause of RSE, anaesthetic(s) used to treat RSE, discharge from ICU, hospital, survival and aSTESS.

| ID | Age | Sex | History of Epilepsy | Type of RSE | RSE Duration (days) | Cause of RSE? | IVAT | D/C from ICU and hospital | Survival 1 / 3 month(s) post RSE | Functional outcome | Adjusted STESS |
|----|-----|-----|---------------------|-------------|--------------------|---------------|------|-------------------------|----------------------------|------------------|----------------|
| 1  | 50  | M   | N                   | BTC         | 1.5                | Right frontal meningioma with edema and midline shift | Propofol | Y                        | Y/Y                        | 1                | 3              |
| 2  | 60  | M   | N                   | BTC, then subtle focal motor S2, then NCSE | 2 | Seizures after cranioplasty for malignant right MCA stroke | Propofol | Y                        | Y                          | 1                | 3              |
| 3  | 28  | F   | Y                   | BTC cluster X 3, then prolonged BTC | 21 | Epilepsy-ASM non compliance | Propofol, Midazolam, Ketamine | Y                        | Y                          | 1                | 2              |
| 4  | 61  | F   | N                   | BTC, then NCSE | 5 | Post aneurysm clipping | Propofol, Ketamine | Y                        | Y                          | 2                | 3              |
| 5  | 74  | M   | N                   | Focal S2, then NCSE | 5 | Frontal intraparenchymal hemorrhage | Propofol | Y                        | Y/Y                        | 1                | 5              |
| 6  | 58  | F   | Y                   | Generalized myoclonus, then NCSE | 12 | Medication induced | Midazolam, Ketamine | Y                        | Y                          | 2                | 3              |
| 7  | 26  | M   | N                   | BTC, then NCSE | 9 | MS lesions | Propofol, Midazolam | Y                        | Y/Y                        | 1                | 3              |
| 8  | 67  | M   | N                   | NCSE | 4 | Subdural empyema, ventriculitis, cerebritis | Propofol | N                        | N                          | n/a              | 5              |
| 9  | 60  | F   | Y                   | BTC, then NCSE | 10 | Epilepsy and left subdural hematoma | Propofol, Midazolam, Propofol, Midazolam | N                        | N                          | n/a              | 3              |
| 10 | 88  | M   | N                   | NCSE | 9 | Right subdural (seizures post-evacuation) | Propofol, Midazolam | N                        | N                          | n/a              | 5              |
| 11 | 81  | F   | N                   | NCSE | 5 | Unclear-post operative | Propofol, Midazolam | N                        | N                          | n/a              | 5              |
| 12 | 71  | F   | N                   | NCSE | 5 | Multifactorial | Propofol, Midazolam | N                        | N                          | n/a              | 5              |
| 13 | 23  | M   | N                   | NCSE | 46 | Traumatic brain injury | Propofol, Midazolam, Ketamine | N                        | N                          | n/a              | 3              |
| 14 | 63  | M   | N                   | NCSE | 12 | Multifactorial | Propofol, Midazolam, Ketamine | N                        | N                          | n/a              | 2              |
| 15 | 81  | F   | Y                   | BTCX2, then NCSE | 2 | Gliosis from prior intracranial hemorrhage | Propofol, Midazolam | N                        | N                          | n/a              | 4              |
| 16 | 73  | F   | N                   | Left hemispheric NCSE | 10 | Right subdural hematoma (seizures post-evacuation) | Propofol, Midazolam, Ketamine | N                        | N                          | n/a              | 5              |
| 17 | 75  | M   | N                   | NCSE | 3 | Acute on chronic subdural hematoma | Propofol, Midazolam, Ketamine | N                        | N                          | n/a              | 5              |

ASM: antiseizure medication, BTC: Bilateral tonic clonic seizure, D/C: discharge, IVAT: intravenous anaesthetic therapy; NCSE: non-convulsive status epilepticus, RSE: refractory status epilepticus, aSTESS: adjusted status epilepticus severity score, S2: clinical seizure; n/a: not applicable; for functional outcome, 1 refers to independent with assistance and 2 refers to dependent.

Fig. 1. Concatenated longitudinal QBSR values per 10-second epoch for all 17 patients over all 160 EEG recording sessions. Each color series represents a different patient.
3.2. QBSR and EEG characteristics

QBSR values per 10 s epochs (Fig. 1) among 17 patients (Supplemental Fig. 1) over 160 recording sessions (Supplemental Fig. 2) numbered 135,765 in total (Supplemental Fig. 3). Median cumulative EEG epoch number for all patients was 4739 with no difference between groups (median favorable 4739 vs. unfavorable 5581.5, \( p = 0.69 \), Fig. 2). Median number of EEG sessions for all patients was 7 with no difference between groups (median favorable 5 vs. unfavorable 7, \( p = 0.66 \)). Median per-session EEG epoch number for all patients was 780 epochs, with significantly more epochs per EEG session in favorable group patients (1074.5 vs. 714, or 3 vs. 2 h, \( p = 0.0089 \)).

3.3. QBSR findings

Median QBSR was 0.597, with the favorable group significantly more suppressed on unadjusted univariate analysis (0.874 vs. 0.474, \( p < 0.001 \)). On multivariate analysis (Fig. 3), however, QBSR did not associate with outcome when adjusted for confounding variables (per-capita OR 0.99, 95% CI 0.96–1.01, \( p = 0.303 \), for different numbers of repeated EEGs between patients (per-session OR 1, 95% CI 0.99–1.01, \( p = 0.934 \), and for different epoch durations in each EEG (per-epoch OR 1, 95% CI 1–1, \( p = 0.99 \)). Rather, higher aSTESS significantly and consistently associated with unfavorable outcomes in all analyses: per-capita (OR 0.76, 95% CI 0.59–0.97, \( p = 0.033 \), per-session (OR 0.24, 95% CI 0.06–0.94, \( p = 0.048 \) and per-epoch (OR 0.69, 95% CI 0.68–0.71, \( p < 0.001 \)). Greater IVAT number was associated with favorable outcome on per-epoch analysis (OR 1.49, 95% CI 1.45–1.54, \( p < 0.001 \), but not on a per-capita (OR 0.85, 95% CI 0.57–1.25, \( p = 0.38 \) or per-session basis (OR 1.49, 95% CI 0.04–2.06, \( p = 0.24 \)). Male gender did not associate with outcome on a per-capita (OR 0.97, 95% CI 0.57–1.66, \( p = 0.92 \), per-session (OR 0.89, 95% CI 0.1–8.09, \( p = 0.96 \), or per-epoch basis (OR 1, 95% CI 1–1, \( p < 0.001 \)).

4. Discussion

On unadjusted analysis, the median QBSR of all pooled siEEG epochs was significantly deeper in the favorable group. Taken at face value, this finding suggests that deeper BS on siEEG may counteract the possibility of breakthrough seizures or BS variability during unmonitored times between recording sessions that could adversely affect RSE patient outcome. However, no significant difference between favorable and unfavorable groups could be shown on adjusted per-capita, per-session, or per-epoch analyses. We believe that deeper suppression in the favorable group on initial analysis was related to significantly longer recording sessions on IVAT (extended by an extra median hour), presumably due to intervention bias from significantly younger age and trend to lower illness severity.

In contrast to QBSR, higher aSTESS was consistently associated with worse outcome on all analyses (i.e. per-capita, per-session, per-epoch), which agrees with expectation (internal validity) and is consistent with the literature (external validity) (Rossetti et al., 2008; Madžar et al., 2016; Ciurans et al., 2018). Similarly, we found that gender was not associated with outcome on any analysis,
which also agrees with expectation (Lv et al., 2017); for example, as gender is not part of the STESS calculation (Rossetti et al., 2008).

Lack of association between QBSR and RSE patient outcome has two dimensions: no association with better outcome, and no association with worse outcome. Although higher QBSR represents deeper EEG suppression, IVAT-mediated EEG suppression may simply be transient and reactive RSE suppression, rather than truly extinction with worse outcome. Although higher QBSR represents deeper EEG suppression, IVAT-mediated EEG suppression may simply be unnecessarily targeted to an arbitrarily high BS level in lieu of cEEG. Instead, emphasis could shift toward customizing IVAT titration for its time-varying, non-suppressive effects on EEG content. Further research can capitalize upon our quantitative and longitudinal approaches to extend this work into cEEG using dynamic amplitude, step, and epoch thresholding of additional quantitative metrics. In the meantime, targeting and following deeper EEG suppression on siEEG is of limited utility in RSE.

4.1. Limitations

Despite 135,765 QBSR values, this study is limited by the small sample size of 17 patients from whom they came. Moreover, these QBSR findings were based on siEEG. Median EEG recording duration was 130 min (2.17 h) and occurred at most daily. While some EEG data may be preferable to no data at all, this study demonstrates the practical limits of siEEG, on which even multiple approaches to a dataset of 135,765 quantitative BS measures do not correlate with outcome. Future studies should consider avoiding siEEG to focus on cEEG in more patients. Even on cEEG, however, BS can be highly variable in the absence of IVAT changes due to pharmacokinetics and pharmacodynamics (An et al., 2018). While EEG may be continuously recorded, reacting to breakthrough seizures or BS variability can be delayed (Moura et al., 2014). Variability in BS and clinical response time may explain conflicted findings in the cEEG literature, with reported associations to worse outcome (Hocker et al., 2013), lower seizure recurrence with no effect on outcome (Phabphal et al., 2018), or no association with successful RSE termination (Johnson et al., 2016). However, these studies used variable singly collapsed BS measures (e.g. into one maximal or averaged value). Future cEEG studies may consider a dynamic quantitative approach, such as QBSR, or novel measures such as the burst suppression probability (BSp), which calculates the BS instantaneously rather than over a defined epoch of time (Chemali et al., 2013). The BSP would provide an even higher level of time-resolution to represent another “stratum” above our per-capita, per-session, and per-epoch analyses.

Another limitation is the automated nature of QBSR calculation. We did not visually re-confirm the 135,765 QBSR values or visually reject artifacts. In our experience, background artifacts affecting QBSR (spuriously 0) were usually at recording start and end. These brief artifact outliers would have been diluted by median per-capita or per-session QBSR, and overwhelmed by all remaining QBSR values on per-epoch analysis. We also believe that automatic QBSR calculation best simulates clinical experience. QEEG is often deployed at the bedside for real-time non-neurophysiologist interpretation and decision-making where there is usually no time to review hours of data, visually reject artifacts, and then re-run QBSR calculations (Ng and Gillis, 2017). Similarly, we chose to maintain the default QEEG software QBSR threshold of 3 µV, step size of 0.5 s, and epoch window of 10 s to mimic real-life practice, but these parameters can be modified in future studies.

5. Conclusion

We used multivariate approaches of both traditional time-invariant and more novel time-varying analyses to consistently find no association between RSE patient outcome and siEEG-recorded QBSR mediated by Ketamine, Midazolam, and/or Propofol. Our findings are corroborated by the re-validation of both the contributory role of STESS, and the non-contributory role of gender in RSE prognostication. These findings are most applicable to the many centers with an siEEG mode of practice where IVAT may be unnecessarily targeted to an arbitrarily high BS level in lieu of cEEG. Instead, emphasis could shift toward customizing IVAT titration for its time-varying, non-suppressive effects on EEG content. Future research can capitalize upon our quantitative and longitudinal approaches to extend this work into cEEG using dynamic amplitude, step, and epoch thresholding of additional quantitative metrics. In the meantime, targeting and following deeper EEG suppression on siEEG is of limited utility in RSE.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge the EEG technologists of the Winnipeg Health Sciences Center for their assistance in operating QEEG software for QBSR value generation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2021.10.003.

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