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RESEARCH ARTICLE

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Early processed electroencephalography for the monitoring of deeply sedated mechanically ventilated critically ill patients

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Abstract

Background: Deep sedation may be indicated in the intensive care unit (ICU) for the management of acute organ failure, but leads to sedative-induced delirium. Whether processed electroencephalography (p-EEG) is useful in this setting is unclear.

Methods: We conducted a single-centre observational study of non-neurological ICU patients sedated according to a standardized guideline of deep sedation (Richmond Agitation Sedation Scale [RASS] between −5 and −4) during the acute phase of respiratory and/or cardio-circulatory failure. The SedLine (Masimo Incorporated, Irvine, California) was used to monitor the Patient State Index (PSI) (ranging from 0 to 100, <25 = very deep sedation and >50 = light sedation to full awareness) during the first 72 h of care. Delirium was assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

Results: The median duration of PSI monitoring was 43 h. Patients spent 49% in median of the total PSI monitoring duration with a PSI <25. Patients with delirium ($n = 41/97$, 42%) spent a higher percentage of total monitored time with PSI <25 (median 67% [19–91] vs. 47% [12.2–78.9]) in non-delirious patients (p .047). After adjusting for the cumulative dose of analgesia and sedation, increased time spent with PSI <25 was associated with higher delirium (odds ratio 1.014; 95% CI 1.001–1.027, $p = .036$).

Conclusions: A clinical protocol of deep sedation targeted to RASS at the acute ICU phase may be associated with prolonged EEG suppression and increased delirium. Whether PSI-targeted sedation may help reducing sedative dose and delirium deserves further clinical investigation.

Relevance to Clinical Practice: Patients requiring deep sedation are at high risk of being over-sedated and developing delirium despite the application of an evidence-based sedation guideline. Development of early objective measures are essential to improve sedation management in these critically ill patients.

KEYWORDS
critical care, delirium, processed electroencephalogaphy, sedation

1 | INTRODUCTION

Clinical guidelines aiming at minimizing sedation are recommended in the intensive care unit (ICU),[1,2] but may not be suitable in patients in whom deep sedation is required for the management of acute cardio-circulatory or respiratory failure.[3] Deep sedation is in turn associated with secondary complications, mainly ICU delirium,[4–6] increased hospital length of stay and long-term neuro-cognitive dysfunction.[7] It is demonstrated that sedation intensity, particularly at the acute ICU phase (first 72 h of mechanical ventilation) entails a particularly high risk of acquired neurological complications.[8–11] In this setting, delirium incidence increases with longer cumulative duration of electroencephalogram (EEG)-suppression.[12–14] Based on these findings, sedation guidelines suggest, through an ungraded statement, the use of a processed EEG (p-EEG) in deeply sedated unresponsive ICU patients as a complement to clinical behavioural scales (Richmond Agitation Sedation Scale, RASS), aiming at optimizing sedative dose and avoiding over-sedation.[1]

Processed EEG is well established for the management of anaesthesia depth,[15,16] using computed parameters derived from quantitative EEG analysis such as the Patient State Index (PSI).[17] Recent data suggest that p-EEG—guided anaesthesia may reduce post-operative delirium.[18–21] While PSI appears to be a good indicator of the level of sedation in mechanically ventilated patients,[22] evidence on the utility of p-EEG in the ICU is limited[23] and needs to be confirmed by objective data.

The objective of this study was to describe the PSI index in deeply sedated critically ill patients with acute organ failure, and to examine a potential association between low PSI values (<25, to define EEG suppression state) and ICU delirium, assessed with the Confusion Assessment Method for ICU (CAM-ICU).

What is known about the topic

- Sedation management influences delirium development
- Objective measurements of deep sedation are lacking

What this paper adds

- Standardized guideline of targeted deep sedation is associated with prolonged EEG suppression and over-sedation, as defined by a Patient State Index below 25
- Longer duration of PSI <25 is associated with higher risk of ICU delirium
- Our single-centre study results prompt further investigation to evaluate whether PSI-targeted sedation may help optimizing sedative dosage, thereby limiting ICU delirium.

2 | METHODS

2.1 | Design, setting, study population

This retrospective single-centre observational study was conducted from January 2018 to December 2020 at the 35-bed general ICU of the Department of Adult Intensive Care, in Lausanne, Switzerland. Participants were mechanically ventilated non-neurological, medical or surgical, adult patients requiring deep sedation (defined as a Richmond Agitation Sedation Scale (RASS) between −5 and −4[24]), because of acute organ failure, who were monitored for at least 12 h with p-EEG, and who had delirium assessment with the CAM-ICU. Patients with primary acute brain injury, cardiac arrest and previous known cognitive impairment were not included. This study was approved by the local human research ethics committee.

2.2 | Management of analgesia and sedation

Analgesia and sedation were managed according to a local standardized guideline in line with current recommendations.[1] This is a nurse-led guideline, where prescribed drug doses are tailored to the patient's target sedation level, using the RASS. Patients were primarily sedated with propofol. When patients received norepinephrine >0.25 μg/kg/min, or propofol exceeded 4 mg/kg/h or was administrated for more than 48 h, sedation was switched to midazolam (0.05–0.15 mg/kg/h). When required, a neuromuscular blockade agent, such as cisatracurium or rocuronium, was administrated in addition to sedatives and analgesics. Analgesia was provided using continuous infusion of fentanyl (1–1.5 μg/kg/h). Additional boluses of analgesia or sedation were administered as needed.

2.3 | Processed EEG

The SedLine Brain Function Monitor (Masimo, Irvine, California, USA) was used as part of standard practice in our ICU to monitor sedation depth in severe critically ill patients, requiring deep sedation because of acute organ failure (including respiratory and cardio-circulatory). The non-invasive SedLine EEG uses symmetrical bi-frontal electrodes to measure 4-channels of raw EEG data with separate displays for electromyogram (EMG), artefacts, the suppression ratio (SR, i.e., percentage of time with suppressed EEG) and density spectral array.

The SedLine monitor also estimates sedative depth from digital EEG waves using a proprietary algorithm and displays a dimensionless parameter called the Patients State Index (PSI), ranging from 0 to 100, with values below 25 indicating severe EEG suppression (very deep sedation), values between 25 and 50 deep-to-moderate sedation, and values above 50 light sedation to full awareness.[25,26]

The PSI monitoring was started by nurses within the first 24 h from ICU admission and lasted up to 72 h, with possible interruptions in between because of care purposes. Of note, sedation and analgesia management were exclusively guided by our standardized guideline. Indeed, pEEG monitoring was performed to collect data, but *PSI data were not taken into consideration into the sedation guideline, because of the lack of evidence to support practice at the time.* PSI values were

thus only recorded for the study purpose and medical clinicians and nurses caring for the patient were blinded to p-EEG data.

2.4 | Delirium assessment

Delirium was assessed by nurses twice daily using the CAM-ICU,[27] once the patient reached a RASS ≥−2 and therefore after p-EEG monitoring, until ICU discharge. Patients were considered to have delirium when the CAM-ICU was positive for at least 2 days based on clinical significance of cognitive decline after 2 days.[28–30] Delirium duration was defined as the total number of days spent with at least one positive daily CAM-ICU assessment. Patients without a CAM-ICU assessment were excluded.

2.5 | Data processing and statistical analysis

Demographic and clinical variables included age, gender, primary admission diagnosis, the Sequential Organ Failure Assessment (SOFA) score on admission, cumulative doses of analgesia (fentanyl) and sedation (propofol and midazolam), duration of mechanical ventilation, length of ICU stay and ICU mortality.

To ensure quality of SedLine data, PSI values were excluded when the artefact percentage was ≥10% and the EMG was >50. The first 5 min of recording after monitoring start, as well as before and after monitor disconnection, were also excluded. For each patient, PSI values were averaged hourly, and we then calculated the total percentage of time spent with a PSI <25 during the monitored time at the acute phase (24–72 h).

Data are presented as mean (standard deviation, SD) or median (interquartile range, IQR) according to the Shapiro–Wilk normality test. Univariate associations between delirium and non-delirium groups were analysed using the Student t-test or the Wilcoxon-Mann–Whitney test for continuous variables, as appropriate, and the Chi-square test for categorical variables. A multivariable stepwise regression analysis was conducted, with the percentage of time spent with PSI <25 as the variable of interest and all variables with a p value <.1 in the univariate analysis were entered asco-variates. Statistical significance was set at $p < .05$. Statistical analyses were performed with SPSS (version 27, SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Patient characteristics

A total of 97 patients were included in the study. Out of the 145 patients assessed for eligibility, 48 were excluded: 25 met the exclusion criteria and 23 could not be assessed for delirium (18 died and 7 were referred to another hospital). Table 1 summarizes the demographic and clinical characteristics of the population.

TABLE 1 Patient characteristics.

Variable	Value
Patient number	97
Age, years	67 (54–73)
Female, *n* (%)	29 (30)
Primary admission diagnosis, *n* (%)	
Respiratory failure	49 (50)
Cardio-circulatory failure	30 (31)
Sepsis	15 (15)
Others (trauma, severe burns, severe haemorrhage, etc)	4 (4)
Admission SOFA score	8 ± 4
Neuromuscular blockade infusion	70 (72)
ICU delirium[a], *n* (%)	41 (42)
Duration of ICU delirium, days	1 (0–3)
Duration of mechanical ventilation, days	9 (6–19)
Length of ICU stay, days	19 (10–27)
ICU mortality, *n* (%)	9 (9)

Note: Data are presented as median (interquartile ranges) or mean ± standard deviation.
Abbreviations: SOFA, sequential organ failure assessment.
[a]Defined as the presence of a positive CAM-ICU for at least 2 days.

3.2 | Processed EEG results

The median PSI monitoring time per patient was 43 h (IQR 31–53). Patients spent a median of 49% (IQR 10–84) of the total PSI monitoring time with a PSI <25. Twenty percent of the total monitoring time was discarded because of the presence of pre-specified criteria for poor signal quality.

3.3 | Associations between low PSI values and ICU delirium

Table 2 shows comparisons of demographic and medical variables between the delirium and the no delirium groups. Patients with ICU delirium received a higher total dose of fentanyl ($p = .017$) and propofol ($p = .003$) during the sedation phase than the no delirium group. There was also a significant longer duration of coma ($p = .008$), mechanical ventilation ($p < .001$) and ICU stay ($p < .001$) in the delirium group, compared with the no delirium group.

Delirium patients spent a significantly higher median percentage of time with a PSI <25 when compared with non-delirious patients (67% [19–91] vs. 47% [12.2–78.9]; $p = .047$, Table 2).

The global PSI distribution across the three predefined PSI categories (average individual % time spent with a PSI at 0–25 = severe EEG suppression/very deep sedation; 25–50 = deep/moderate sedation; >50 = light sedation/full awareness) in patients with or without delirium is shown in Figure 1.

Variable	Delirium ($n = 41$)	No delirium ($n = 56$)	p value
Admission demographics			
Age, years	65 (53–75)	68 (55–72)	.962
Female, *n* (%)	9 (22)	20 (36)	.144
SOFA on admission	8 ± 4	8 ± 3	.551
Sedation and analgesia dose			
Cumulative fentanyl dose (μg/kg)	260 (102–519)	122 (63–295)	**.017**
Cumulative propofol dose (mg/kg)	545 (247–974)	268 (77–491)	**.002**
Cumulative midazolam dose (mg/kg)	5 (1–11)	2 (0–8)	.057
Processed EEG data			
Median time spent with PSI <25, %	67 (19–91)	47 (12–79)	**.047**
ICU outcomes			
Duration of mechanical ventilation, days	14 (8–27)	8 (5–14)	**<.001**
Duration of ICU stay, days	24 (18–36)	13 (8–20)	**<.001**
ICU mortality	4 (10)	5 (9)	.890

TABLE 2 Characteristics of patients with and without delirium.

Note: Data are presented as median (interquartile ranges) or mean (standard deviation).

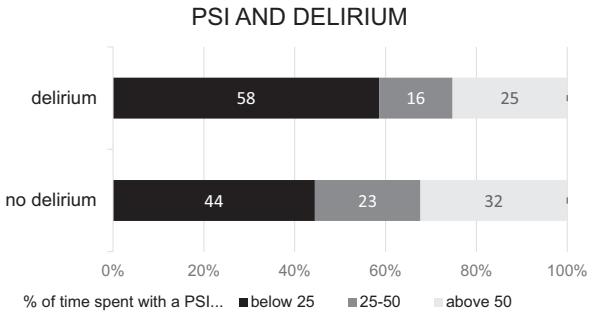

FIGURE 1 Average percentage of time spent at the different PSI ranges in patients with vs. without delirium.

3.4 | Increased percentage of time spent with a PSI <25 was independently associated with delirium

By multivariable analysis, after adjusting for the cumulative dose of fentanyl, propofol and midazolam, increased time spent with a PSI <25 was significantly associated with a higher rate of ICU delirium (odds ratio 1.014; 95% confidence interval 1.001–1.027, p .036 – Table 3). *No association between the PSI <25 and the analgo-sedation variables was found by bivariate analysis (PSI <25 and cumulative fentanyl p .53; PSI <25 and cumulative propofol p .54; PSI <25 and cumulative midazolam p .93).*

4 | DISCUSSION

This study investigated the potential utility of p-EEG, specifically using PSI monitoring at the acute ICU phase, in medical-surgical critically ill patients, without primary brain injury or known cognitive impairment, who required deep sedation for the management of cardio-circulatory and respiratory failure.

In our cohort, the incidence of delirium is less than in other studies, 42% versus 55%.[31,32] This rate is somewhat lower because we defined delirium as two or more days with positive CAM-ICU: this allowed us to test the utility of PSI in the population with higher risk of adverse consequences induced by the longer duration of ICU delirium. The characteristics of our cohort are similar to previous descriptions in the literature, with higher severity disease,[32,33] higher analgesia and sedative doses,[31,32,34] longer mechanical ventilation and longer ICU stay.[32]

The patients of our sample spent half of their monitoring time with a PSI <25, that is, in state of EEG suppression, during the early phase of the critical illness. Below the threshold of 25, the level of sedation is considered to be beyond requirements of general anaesthesia, corresponding to over-sedation.[35] Critical care nurses play a key role in the monitoring and management of sedation, aiming at minimizing over-sedation and improving patient care and outcomes.[36] The application of standardized sedation based on valid subjective sedation scales may not be sufficient to prevent over-sedation and potentially related delirium. Indeed, this was indicated by our data showing that many patients in our cohort were over-sedated. Our results, therefore, support the value of a p-EEG as complementary quantitative tool for the management of deeply sedated ICU patients, and the instrumental role of critical care nurses in this setting. Regular (at least every 4 h) clinical sedation assessment in combination with a p-EEG quantitative monitoring may offer additional information and improve nursing assessment, potentially achieving a higher degree of accuracy in detecting over-sedation. In summary, p-EEG appears to be a useful technology in deeply sedated patients because (a) it allows calculation of an objective quantitative index that accounts for the effect of drugs on brain activity, (b) it gives indications of deeper ranges of sedation once the patient is unresponsive; and (c) it complements standard sedation assessment and may be useful to nursing care of deeply sedated critically ill patients, particularly at the early phase, where no validated objective tool is available.

TABLE 3 Association between PSI and ICU delirium adjusted by analgesia and sedation dose.

Variable	Odds ratio	95% confidence interval	*p* value
% of time with a PSI <25	1.014	1.001–1.027	**.036**
Cumulative fentanyl (μg/kg)	1.000	0.997–1.003	.838
Cumulative propofol (mg/kg)	1.001	1.000–1.002	.120
Cumulative midazolam (mg/kg)	0.992	0.979–1.007	.292

International guidelines and panels of experts advocate reducing the type and dose of sedation which is recognized to have an impact on ICU patient outcomes.[1,2] The hypothesis that higher drug use increases the risk of delirium has been widely tested but results are inconsistent. Although a meta-analysis showed a two-fold increase in the incidence of delirium in early deeply sedated patients compared with lightly sedated patients, no statistical difference could be established.[8] Similarly, a recent meta-analysis showed no relationship between the depth of sedation and delirium in ICU patients.[37] Two recent randomized controlled trials examined the effect of PSI-guided anaesthesia versus routine care on delirium, and again the results are controversial. In the first study, including 1560 patients aged >50 years undergoing laparoscopic surgery, PSI-guided care did not reduce delirium (RR 0.90; 95% CI:0.69–1.17; $p = .41$).[38] In the second study on the contrary, including 255 patients undergoing carotid endarterectomy, PSI-guided anaesthesia resulted in lower incidence of post-operative delirium (p .01).[21] Similarly to what was observed with the PSI, p-EEG data using the BIS index in surgical patients also found controversial results; the ENGAGES study showing that BIS-guided anaesthesia did not reduce delirium (difference 3%; CI 95% −2%–8%; $p = .22$), while the BALANCED sub-study resulted in a decreased incidence of delirium (odds ratio 0.58; CI 95% 0.38–0.88; $p = 0.01$).[39,40] Despite controversial results on delirium outcomes, all demonstrated a lack of relationship between the anaesthesia dose and delirium. However, in this respect, an important confounding factor needs to be taken into account, that is, for the same sedation dose, the individual quantitative EEG response (PSI or BIS change) varies largely across patients. Use of a mixed-effects model to adjust for the individual dose–response variability is advised[41,42] and may serve future investigation to better identify those patients for whom sedation is a clear risk factor for delirium (i.e., greater sensitivity = low sedative dose, large effect on EEG indexes) from those in whom sedation has reduced risk of secondary delirious complications (i.e., lower sensitivity = high sedative dose, small effect on EEG indexes).

5 | LIMITATIONS

This study has several limitations. First, it was single centre, with a convenience sample and without formal sample size calculation, making the data non generalizable. However, the cohort is representative of the most critically ill patients, with the highest delirium risk[4] and where PSI monitoring may be of greatest interest.[1] Second, we used a standardized guideline, indicating the use of propofol or midazolam according to the patient's clinical situation and this makes it difficult to interpret the influence of the drugs used on the PSI. In addition, the need for a neuromuscular blockade infusion was frequent but not the same across the sample. Adherence to sedation guideline was not recorded during the study period. However, monitoring of the sedation guideline in the first 6 months post-implementation showed that the maximum recommended doses of sedatives were provided as per guideline.

6 | CONCLUSION

This study showed that ICU patients with cardio-circulatory or respiratory failure are over-sedated, according to a PSI <25, despite applying a sedation-targeted guideline including predefined analgesia and sedative doses. We also observed that a higher percentage of time spent with a PSI <25 on early deep sedation requirement may be associated with delirium, regardless of the analgesic and sedative doses administrated. The findings of this study prompt further investigation to validate the use of processed EEG in the ICU.

AUTHOR CONTRIBUTIONS

Eva Favre wrote the protocol, performed the data collection, the statistical analyses and drafted the manuscript. Adriano Bernini performed the data processing, was involved in the statistical analyses and critically revised the article. John-Paul Miroz collected the data and critically revised the article. Samia Abed-Maillard conducted protocol development, submission and regulatory aspects and critically revised the article. Anne-Sylvie Ramelet was involved in the study supervision and critically revised the manuscript. Mauro Oddo designed and supervised the study, was involved in manuscript drafting and revision. All the authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the local human research ethics committee (project-ID 2021–02026).

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