Electroencephalogram Features and Postoperative Neurocognitive Disorder

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Postoperative neurocognitive disorder (PND) is a common postoperative complication, particularly in older patients. Electroencephalogram (EEG) monitoring, a non-invasive technique with a high spatial–temporal resolution, can accurately characterize the dynamic changes in brain function during the perioperative period. Current clinical studies have confirmed that the power density of alpha oscillation during general anesthesia decreased with age, which was considered to be associated with increased susceptibility to PND in the elderly.

1. Introduction

The development of medical services with the ageing population has become an important issue worldwide. Each year, over 19 million patients aged ≥65 years undergo surgery under general anesthesia [1]. Perioperative neurocognitive disorders (PND), a type of common neurological complication, occurred in up to 50% of elderly patients undergoing major or high-risk operations, such as hip-fracture repair and cardiac surgery [2][3]. The category of PND includes: (1) cognitive decline diagnosed before operation (described as neurocognitive disorders); (2) postoperative delirium (POD); (3) delayed neurocognitive recovery to 30 days; and (4) postoperative neurocognitive disorder up to or beyond 12 months [4]. PND not only prolongs hospital stays and increases hospital costs, but also significantly increases mortality and the incidence of dementia [5]. Hence, neuroscientists and anesthesiologists have long been committed to developing a series of reliable, fast, and safe techniques to provide an early warning of neurological damage within the perioperative period both accurately and sensitively, so as to prevent or ameliorate the risk of PND.

The electroencephalogram (EEG) is a kind of non-invasive technique, which accurately characterizes the dynamic changes in brain function with a high spatial–temporal resolution. In the past few decades, processed EEG (pEEG) monitors based on the electrical activity of the frontal cortex have been widely used in clinical practice [6]. pEEG indices are quantitative parameters generated by translating the EEG signal into an index of anesthetic depth ranging between 0 (isoelectric EEG) and 100 (fully awake) [7], such as the bispectral index (BIS) and patient state index (PSI). However, evidence from recent clinical studies has shown that the intraoperative monitoring of the depth of anesthesia via a commercial dimensionless index cannot effectively identify the pathological change in the brain [4]. EEG characterizes the multi-dimensional information of the brain state, including power spectrum, complexity, and functional connection between different brain regions, which can reflect the function of the whole brain. Researchers suggest that more comprehensive information generated by the raw data of multi-channel EEG will contribute to finding the biomarkers of PND that have been ignored in previous studies. For example, as researchers need to recognize the impairment of brain function, researchers could characterize the disintegration of EEG signals from different regions to account for the breakdown of neural networks [8].

2. Intraoperative EEG Features and PND

2.1. Processed Electroencephalography Indices

A large amount of work has investigated whether the pEEG-guided dosing of general anesthetics can improve postoperative outcomes. For instance, in the Cognitive Dysfunction after Anesthesia (CODA) trial, Chan et al. [9] aimed to determine whether the use of BIS could decrease the incidence of POCD. A total of 921 patients (≥60 years old) undergoing major non-cardiac surgery were randomly assigned to receive either BIS-guided anesthesia, where anesthesiologists were instructed to target a BIS value between 40 and 60 during general anesthesia, or routine care, where BIS was monitored but not revealed to anesthesiologists. Postoperative cognitive decline at 3 months was found to be reduced in the BIS-guided group compared with the routine care group. A meta-analysis of 13 trials identified that

pEEG-guided anesthesia could reduce the incidence of POD [10]. Similarly, Punjasawadwong et al. [11] found that EEG-guided anesthesia, such as BIS, ameliorated POD, POCD and their consequences in patients undergoing non-cardiac surgery with moderate-quality evidence. Patients included in this meta-analysis underwent a variety of procedures, from ambulatory surgery to major non-cardiac surgery. Previous studies about the relationship between the depth of anesthesia and PND have focused on comparing BIS-guided general anesthesia with routine care; however, the sub-study of the Anaesthetic depth and complications after major surgery (BALANCED) trial explored whether lighter general anesthesia could decrease the incidence of POD. They included 547 patients 60 years and older, undergoing elective surgery expected to last at least 2 h, who were randomized to receive BIS target 50 (light general anesthesia) or BIS target 35 (deep general anesthesia). POD was detected in 19% of the patients in the BIS target 50 group, compared with 35% in the BIS target 35 group ($p = 0.010$). The main finding was that light general anesthesia could decrease the incidence of POD in the elderly [12].

Many randomized controlled trials (RCTs) and meta-analyses reported that pEEG-guided care was able to decrease the incidence of POD or POCD, mainly depending on the reduction in anesthetic exposure and duration of EEG suppression [9][13]. However, recently, the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial [14] did not support the use of pEEG monitoring to reduce the risk of POD. In the ENGAGES trial, 1232 patients aged 60 years or older scheduled for major surgery under inhaled anesthesia were randomized to receive either EEG-guided anesthetic administration or standard anesthetic care. The incidence of POD was not significantly different between the two groups (26% vs. 23%; difference = 3%; 95% CI, −2.0% to 8.0%; $p = 0.22$). This result showed that the pEEG guidance of anesthesia in elderly adults did not reduce the incidence of POD. The ENGAGES trial has admitted having several problems, including the lack of a clinically relevant difference in general anesthetic concentration between groups (0.69 vs. 0.80 MAC). At the same time, the median time difference between groups with EEG suppression was small (7 vs. 13 min). In addition, the prevalence of POD was higher than in other trials because the patients were highly susceptible to developing POD. Therefore, pEEG monitors probably do not prevent POD in highly susceptible patients, but this does not mean that EEG-based anesthesia guidance does not prevent POD. Recently, Sun et al. [15] published an updated meta-analysis of five trials with a sum of 3612 patients; the result did not support the preventive effect of pEEG-guided anesthesia on POD. However, they performed a thorough sensitivity analysis which showed that the ENGAGES trial accounted for 30% of the data in the meta-analysis and can be viewed as an outlier in relation to the other trials. Although protocols using pEEG indices to titrate drug effect have had discordant results on PND rates, intraoperative pEEG indices have been investigated to avoid POD and other sorts of PND in elderly patients.

pEEG indices could be affected by anesthetics, age, and preoperative cognitive status in older patients, so it was difficult to consider these indices as independently predictive for neuro-outcomes such as POD [6]. In a large single-center cohort with 4699 patients aged >30 years receiving general anesthesia with volatile anesthetics, Ni et al. [16] reported that the elderly received higher age-adjusted minimum alveolar concentration (MAC) fractions of volatile anesthetics but displayed increased BIS values compared with the young ($\rho = 0.15$; 95% CI: 0.12–0.17; $p < 0.001$). The BIS values in aged patients were paradoxically higher than those in younger patients. Moreover, BIS values increased with the administration of nitrous oxide or ketamine [17][18], underestimating the true depth of anesthesia. Therefore, BIS monitoring might be an inaccurate measurement of the effect of anesthetics in elderly adults which may lead to an incorrect exaggeration during general anesthesia, especially in the elderly.

2.2. EEG Spectral Analysis

Due to the limitation of pEEG in anesthesia monitoring, researchers have attempted to utilize unprocessed EEG to monitor and assess brain activity. Recent guidelines from Perioperative Quality Initiative recommend that anesthesiologists learn to interpret basic EEG, such as the raw waveform and spectrogram, to decrease the incidence of PND [19]. Researchers review the recent findings of important EEG features related to the occurrence of PND, including decreased alpha power, burst suppression, and EEG connectivity and complexity.

2.2.1. Alpha Band Activity

The frequencies of raw EEG signal always range from 0.3 to 45.0 Hz and can be divided into five bands according to amplitude and frequency [20]. The alpha band (8–13 Hz) is of particular interest because it changes with age during general anesthesia. Purdon et al. [21] investigated the influence of age on EEG spectral distribution during general anesthesia. The EEG spectra in young (18–38 years old) and elderly (70–90 years old) patients that received propofol or sevoflurane anesthesia were compared throughout a 2 min period of stable anesthetic maintenance. The results showed that EEG power across all frequency bands declined significantly with increasing age during the stable maintenance of anesthesia, and the change in alpha power was much more significant than that in other frequencies. The age-related decrement in alpha power might be derived from the decline in central synaptic density, changes in dendritic dynamics,

and the reduction in neurotransmitters within the cerebral cortex [22][23]. These findings also reflect the underlying alterations in the properties of neural circuits with regard to alpha oscillation generation. Alpha power is thought to originate from thalamocortical electrical transmission [24], and participates in the modulation of arousal, attention, and other important cognitive functions. As a result, alpha power has been the subject of several studies investigating the biomarkers of neurocognitive decline during the perioperative period.

2.2.2. Alpha Power and Preoperative Cognitive Decline

Preoperative cognitive function is associated with distinct EEG changes in the alpha band during anesthesia induction. Cartailler et al. [25] initially established an association between transient amplitude decreased (TAD) and cognitive status in a prospective study involving 38 patients (>50 years old) undergoing orthopedic surgery or neuroradiology intervention. The authors assessed cognitive function before surgery using the Montreal Cognitive Assessment method (MoCA). The target concentration of propofol (TCI) was set to 5 µg/mL during the induction of general anesthesia. They found that lower preoperative MoCA scores were linked to a rapid TAD increase and an alpha power decrease measured during the first 10 min of propofol-induced general anesthesia. Furthermore, the slope of TAD was related to the patient's cognitive performance. Measuring the TAD slope at the onset of general anesthesia could indicate whether patients have cognitive impairment in the preoperative setting.

Elderly patients with cognitive decline in the preoperative setting have also been demonstrated to exhibit less intraoperative frontal alpha power during the maintenance of anesthesia. In an observational prospective cohort study, Giattino et al. [26] enrolled 50 patients aged 60 and older undergoing non-cardiac, non-neurologic surgery under propofol or isoflurane anesthesia They assessed preoperative neurocognitive function using their well-established neurocognitive test battery, and then measured the average alpha power using 32-channel EEG or BIS monitoring. The analysis of the EEG recordings from 15 patients who underwent 32-channel EEG and from 35 patients underwent single-channel prefrontal EEG using the BIS monitoring identified a significant association between intraoperative frontal alpha power and preoperative cognitive index score (rs = 0.593, p = 0.022; rs = 0.338, p = 0.047, respectively). In all cases, intraoperative frontal alpha power was correlated with preoperative cognitive performance in 50 elderly patients anesthetized with propofol or isoflurane. However, such a relationship between frontal alpha power and preoperative cognitive function was not observed in other EEG frequency bands. Gutiérrez et al. [27] demonstrated that patients with lower MoCA scores exhibited lower alpha power and slower alpha peak frequency, which is consistent with the possibility that elderly patients with poor cognitive function receive an overdose of brain anesthesia compared to cognitively more robust patients. Similarly, Touchard et al. [28] included 42 patients who had a preoperative cognitive assessment using MoCA with EEG information collected under a propofol-based general anesthesia, and they found that patients with cognitive decline had a lower alpha power and target TCI. Both articles demonstrate that preoperative cognitive status is associated with the sensitivity of the effect of general anesthetic. Thus, patients with some degree of cognitive impairment are more sensitive to the effect of general anesthetic, expressed as a greater slowing of EEG activity at the same anesthetic dose than in a cognitively more robust patient. Unable to show significant frontal alpha power under general anesthesia might be used as an intraoperative electrophysiological phenotype of preoperative cognitive decline. Meanwhile, from a prospective observational cohort study of 38 patients aged 65 and over undergoing elective surgery, as reported by Koch et al. [29], patients with reduced cognitive function presented a lower intraoperative alpha power. In contrast, the baseline of frontal alpha power in the preoperative period showed no correlation with preoperative overall cognitive function. Although cognitive decline was associated with reduced frontal alpha power in the resting brain [30], the authors found no correlation between baseline alpha power and preoperative cognitive performance. These studies indicate that age-dependent changes in cerebral activity are more sensitive for predicting cognitive function under general anesthesia than some other status. In summary, anesthesia-induced frontal alpha activity was related to poorer preoperative cognitive performance in elderly patients.

2.2.3. Alpha Power and Postoperative Cognitive Decline

Intraoperative alpha power was also correlated with postoperative neurocognitive function. In order to investigate the potential intraoperative EEG patterns correlated with POD and subsyndromal delirium (PSSD), Gutierrez et al. [31] conducted an observational exploratory study, which included 36 patients aged 60 and older scheduled for elective major abdominal surgery. POD or PSSD was measured by the CAM instrument after surgery, and EEG signals were collected by a 16-channel EEG before and during the administration of inhaled anesthetics. They found that subjects in the POD/PSSD group compared with the control group had reduced intraoperative absolute (4.4 ± 3.8 dB vs. 9.6 ± 3.2 dB, p = 0.0004) and relative alpha power (0.09 ± 0.06 vs. 0.21 ± 0.08, p < 0.0001). Additionally, relative alpha power was able to identify patients with reduce cognitive function with an area under the curve of 0.90 (CI 0.78–1, p < 0.001). This phenomenon suggested that the thalamocortical feedback mechanism associated with intraoperative alpha power was disrupted in patients with POD or PSSD [32]. The susceptibility of POD or PSSD was unmasked under the effects of

general anesthetics. The reduced intraoperative alpha power could be utilized as a novel EEG biomarker to identify patients with a high risk of POD or PSSD.

In summary, such works have validated that decreased alpha power during the maintenance and induction of anesthesia may predispose patients to cognitive decline during the perioperative period, forming the basis for the suggestion that the "manipulation of alpha power during general anesthesia may prove to enhance early neurocognitive recovery in older adults" [33][34]. It is also suggested that EEG-guided dosing of general anesthetics to generate the desired alpha oscillation would be able to minimize the incidence of PND. Further studies should identify the clinical utility of the unprocessed EEG and its spectrogram to individualize the dose of anesthetic required for elderly patients.

2.3. Burst Suppression (BS)

Under the deep state of unconsciousness induced by anesthetic drugs, burst suppression is composed of alternations between isoelectricity and brief bursts of EEG signal [35]. In actuality, evidence on the occurrence of burst suppression and PND is controversial.

2.3.1. Burst Suppression Is Detrimental for POD

Some studies have demonstrated that intraoperative EEG burst suppression and duration predicted POD. In a prospective clinical trial, Fritz et al. [36] included 727 patients receiving volatile-based general anesthesia. They assessed POD using CAM-ICU on postoperative days 1 through 5 and measured the burst suppression obtained from BIS monitoring. POD was more likely to develop in patients who experienced more suppression($\chi^2(4) = 25$; $p < 0.0001$). A correlation was demonstrated between intraoperative burst suppression and POD in a multivariate regression analysis after adjusting for potential confounders (OR = 1.22; 99%CI, 1.06–1.40; $p = 0.0002$). Similar findings were reported by Momeni et al. [37] in a prospective study that enrolled 1515 patients scheduled for cardiac surgery or transcatheter aortic valve implantation (TAVI). Recently, a prospective observational study of 81 subjects undergoing cardiac surgery [38] showed that delirious patients stayed in a burst suppression state for much longer than non-delirious patients (107 min, IQR [47;170] vs. 44 min, IQR [11;120], $p = 0.018$). Pedemonte et al. [39] included 159 subjects aged >60 years scheduled for cardiac surgery with CPB. They evaluated POD using the long version of the CAM and measured burst suppression by analyzing EEG data in the spectral and time-series domains. POD was identified to be more prevalent in subjects with CPB burst suppression compared with the subjects without CPB burst suppression (25% vs. 6%). In a multivariate logistic model, burst suppression was found to be an indicator of POD (OR = 4.1,95%CI 1.5–13.7, $p = 0.012$). A retrospective observational study by Lele et al. [40], which included 112 subjects aged between 20 and 88 years old undergoing spine instrumentation surgery with total intravenous anesthesia (TIVA), similarly adds to researcher's understanding. They found that the incidence of intraoperative burst suppression was higher in subjects who developed POD (100% vs. 66.7%; $p = 0.03$, RR: 1.5, 95% CI: 1.3–1.7). Above all, intraoperative burst suppression activity could indicate a deep stage of anesthesia, which may trigger the development of POD in the elderly.

Furthermore, POD is more prevalent in patients who experienced burst suppression at a relatively low volatile anesthetics dose, which was identified by Ackland et al. [41] in a pivotal discussion about the ENGAGES trial. A retrospective analysis of 618 adult subjects who underwent general anesthesia for elective surgery reported by Fritz et al. [42] also found that EEG suppression at a lower inhaled anesthetics dose resulted in a higher incidence of POD in an adjusted logistic regression model (adjusted OR: 2.13,95% CI 1.24–3.65, $p = 0.006$). Besides, this phenotype is likely to be a more sensitive indicator of POD than the duration of intraoperative burst suppression [43].

In summary, the above studies all demonstrated that EEG suppression is an independent risk factor for POD, and that anesthesia-induced burst suppression may be a potential mechanism resulting in postoperative cognitive impairment. However, it is unclear whether there is a causative correlation between intraoperative burst suppression and POD, or burst suppression simply reflects the patient's susceptibility to POD. If burst suppression is the cause of POD, then EEG-guided low-dose anesthesia that decreases the incidence of intraoperative burst suppression could reduce the risk of POD. However, if burst suppression solely reflects a patient's potential susceptibility to POD, then researchers should identify patients who are susceptible to intraoperative burst suppression early in order to prevent or ameliorate this condition.

2.3.2. Burst Suppression Is Protective or Has No Effect on POD

Contrary to the adverse impact of burst suppression, some studies have suggested that monitoring burst suppression has no effect on postoperative cognitive function, or that burst suppression may be protective. In the ENGAGES study, in contrast to findings from the preceding studies, the authors reported they did not find a statistically significant difference in the incidence of POD between the two groups [14], despite the duration of both EEG suppression (time with BIS < 40

decreased from 60 min to 32 min) and anesthetic dose (median end-tidal anesthesia concentration reduced from 0.8 to 0.7 MAC) being reduced. Similarly, the results of the Anesthetic Depth and Postoperative Delirium Trial-2 (ADAPT-2) trial did not find that decrease in the duration of EEG suppression provided any benefits with regard to the attenuation of the risk of POD (17% vs. 20%, p = 0.53) [44]. Previous studies have linked intraoperative burst suppression to POD, yet modestly shortening the time with EEG suppression had not been demonstrated to decrease the incidence of POD.

In a retrospective observational cohort of 105 subjects aged over 68 years undergoing major non-cardiac surgery, Deiner et al. [45] reported that the duration of burst suppression was shorter in subjects who developed POCD (35 [88] minutes vs. 96 [131] minutes; p = 0.04). The results are similar to a study conducted by Valchanov et al. [46], who found that deep state of anesthesia was protective against POCD. Recently, Shortal et al. [47] studied 27 healthy humans anesthetized with isoflurane 1.3 MAC for 3 h. They recorded the duration of burst suppression and then assessed cognitive impairment using independent cognitive tests. Contrary to current assumptions, in healthy volunteers, the amount of burst suppression had no correlation with the degree of impairment in cognitive performance at emergence. That is, in healthy adults, EEG suppression was not a significant determinant of cognitive impairment after general anesthesia, but whether this finding holds true in elderly patients requires further verification.

Different algorithm values have been utilized to replace the examination of visual burst suppression [48]. Given the differences in the methods used to quantify burst suppression in the observational studies and RCTs described above, it is difficult to draw a consistent conclusion when comparing the results of these studies. Further research is needed to explore the causality between intraoperative EEG burst suppression and PND.

2.3.3. Burst Suppression and Alpha Band Activity

The anesthesia-induced frontal alpha oscillation was not independent of burst suppression. Shao et al. [49] studied burst suppression and a decline in anesthesia-induced frontal alpha power from a trial where 155 patients were under propofol and sevoflurane anesthesia. By using logistic regression, they observed an important association between a reduction in the intraoperative frontal alpha power and an increased propensity of burst suppression. Moreover, they discovered that for each decibel reduction in alpha power, the likelihood of experiencing burst suppression increased by 1.33-fold. The correlation between burst suppression and alpha power was similarly reported by Plummer et al. [50]. The authors analyzed a sum of 138 EEG recordings obtained during general anesthesia from their database and found that reduced EEG power between 7.8 and 22.95 Hz for the maintenance phase of anesthesia was linked to the incidence and duration of burst suppression. As reduced alpha and beta power preceded the onset of burst suppression, their results imply that intraoperative EEG oscillations within the alpha and beta range may be further developed as EEG biomarkers for burst suppression. An intraoperative lower alpha power is significantly correlated with a higher probability for burst suppression and, therefore, an increased risk of PND. More deeply, the EEG alpha power reflects the integrity of cortical and cognitive circuits, and burst suppression is likely to occur in patients with damaged cortical and cognitive circuits. Hence, both intraoperative burst suppression and lower alpha power can be used to characterize brain vulnerability.

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