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ORIGINAL RESEARCH

Electroencephalographic guided propofol-remifentanil TCI anesthesia with and without dexmedetomidine in a geriatric population: electroencephalographic signatures and clinical evaluation

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Abstract
Elderly and multimorbid patients are at high risk for developing unfavorable postoperative neurocognitive outcomes; however, well-adjusted and EEG-guided anesthesia may help titrate anesthesia and improve postoperative outcomes. Over the last decade, dexmedetomidine has been increasingly used as an adjunct in the perioperative setting. Its synergistic effect with propofol decreases the dose of propofol needed to induce and maintain general anesthesia. In this pilot study, we evaluate two highly standardized anesthetic regimens for their potential to prevent burst suppression and postoperative neurocognitive dysfunction in a high-risk population. Prospective, randomized clinical trial with non-blinded intervention. Operating room and post anesthesia care unit at Hospital Base San José, Osorno/Universidad Austral, Valdivia, Chile. 23 patients with scheduled non-neurologic, non-cardiac surgeries with age > 69 years and a planned intervention time > 60 min. Patients were randomly assigned to receive either a propofol-remifentanil based anesthesia or an anesthetic regimen with dexmedetomidine-propofol-remifentanil. All patients underwent a slow titrated induction, followed by a target controlled infusion (TCI) of propofol and remifentanil (n = 10) or propofol, remifentanil and continuous dexmedetomidine infusion (n = 13). We compared the perioperative EEG signatures, drug-induced changes, and neurocognitive outcomes between two anesthetic regimens in geriatric patients. We conducted a pre- and postoperative Montreal Cognitive Assessment (MoCa) test and measured the level of alertness postoperatively using a sedation agitation scale to assess neurocognitive status. During slow induction, maintenance, and emergence, burst suppression was not observed in either group; however, EEG signatures differed significantly between the two groups. In general, EEG activity in the propofol group was dominated by faster rhythms than in the dexmedetomidine group. Time to responsiveness was not significantly different between the two groups ($p = 0.352$). Finally, no significant differences were found in postoperative cognitive outcomes evaluated by the MoCa test nor sedation agitation scale up to one hour after extubation. This pilot study demonstrates that the two proposed anesthetic regimens can be safely used to slowly induce anesthesia and avoid EEG burst suppression patterns. Despite the patients being elderly and at high risk, we did not observe postoperative neurocognitive deficits. The reduced alpha power in the dexmedetomidine-treated group was not associated with adverse neurocognitive outcomes.

Keywords Geriatric · Titration · Propofol · Dexmedetomidine · EEG

1 Introduction

The number of elderly patients undergoing major surgical interventions with general anesthesia is steadily increasing, globally. Due to age-related changes, this patient cohort is at high risk for adverse postoperative outcomes [1, 2]. One major complication after surgery and general anesthesia in elderly patients with multiple comorbidities is neurocognitive dysfunction that can manifest in different forms and severity. [3–5] Such patients may present with emergence delirium in the post-anesthesia care unit (PACU) or develop long-lasting postoperative cognitive dysfunction (POCD) [6]. The incidence of perioperative neurocognitive dysfunction is generally high, ranging from 20 to 60% [7, 8], and carries significant socioeconomic

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burden [9]. For these reasons, strategies to prevent these unfavorable neurocognitive outcomes are urgently needed.

Over the last decade, accumulating evidence suggests that early signs of cognitive dysfunction, e.g. PACU delirium, are associated with adverse long-term effects [10–12]. The origin of these cognitive disturbances is multifaceted and continues to be a subject of ongoing debate. The predictive validity of cognitive tests, the ideal pharmacokinetic/pharmacodynamic modelling (PKPD) approach, the appropriate combination of drugs, the impact of each drug's administration rate, and the identification of optimal electroencephalogram (EEG) patterns for tailoring anesthetic management in elderly patients remains incompletely understood. Early cognitive dysfunction in the PACU may be the result of overdosage and/or an inadequate process of reconnection to the environment, while POCD may be more influenced by metabolic and neuroinflammatory phenomena [13].

One strategy to optimize anesthetic dosages and improve anesthesia quality is to monitor the patient's EEG [14]. Monitoring the EEG can help avoid burst suppression patterns, which potentially correlate with unfavorable outcomes [15–18]. However, the processed EEG indices used in commercial monitoring systems may be insufficient as they do not include age as a covariate [19–21]. One suggested approach is to take the raw EEG and its spectral properties into account when treating the elderly and cognitively impaired patients [22, 23]. For example, the conventional method of inducing loss of responsiveness (LoR) through a standard propofol bolus eliminates the opportunity for tailoring the anesthetic to individualized requirements. Due to the non-linear behavior of the brain under general anesthesia drug dosing might challenging, emphasizing the need for EEG monitoring to avoid pathological brain states such as burst suppression [24, 25].

A combination of slow anesthesia induction using target controlled infusion (TCI) and EEG monitoring can help identify individual anesthetic requirements to properly induce and maintain anesthesia [26]. Another approach would be to take advantage of the greater intrinsic inertia response and to enhance it with a drug that does not have anticholinergic effects and does not directly affect cortico-cortical connectivity, such as dexmedetomidine [27–29]. Dexmedetomidine has long been used as a sedative in intensive care medicine for its anti-neuroinflammatory effects. It also permits the use of lower doses of propofol and mitigates anticholinergic effects on integration networks [30, 31]. So far, we are not fully aware of how the anesthetic combination of propofol and dexmedetomidine influences the EEG and if it impacts the development of immediate postoperative cognitive dysfunction in aged patients.

Currently there is only scarce knowledge about the appropriate combination of these drugs to generate hemodynamic stability while also maintaining adequate levels of disconnected consciousness or unconsciousness.

The occurrence of abnormal and potentially harmful EEG patterns, such as burst suppression, remains a challenge for clinical anesthesiologists. Here we use the frontal Density Spectral Array (DSA) to titrate anesthesia in a vulnerable patient population to overcome difficulties of predictive pharmacological modelling. This pilot study aims to describe perioperative EEG patterns in a high-risk population of two highly standardized regimens. Furthermore, it will evaluate the potential of these two regimens to prevent burst suppression and assess preoperative and immediate postoperative cognitive conditions. Hence, the aims of this pilot study were:

(a) to describe perioperative EEG patterns of two anesthesia regimens with either a propofol-remifentanil induction or a dexmedetomidine-propofol-remifentanil induction.
(b) to evaluate the differences in EEG patterns between the groups and describe their clinical relevance.
(c) to detect signs of emergence delirium in the PACU to put it in context of the two compared anesthetic regimens.

2 Methods

We conducted the pilot study with the approval of the research ethics committee of the Universidad Austral de Valdivia and it was registered in Clinical Trials under the number NCT05425069. The study design was a prospective randomized clinical trial with non-blinded intervention (propofol or propofol and dexmedetomidine anesthesia administration). Each patient gave written informed consent. Included patients were scheduled for elective surgery in Hospital Base San José de Osorno, Chile.

Eligibility criteria were patients classified as physical status ASA I–III and age > 69 years scheduled for non-neurosurgical procedures with estimated duration longer than 60 min. The exclusion criteria were neurological or systemic diseases affecting the central nervous system secondarily; abnormal admission neurological physical exam; consumption of benzodiazepines, tricyclic antidepressants, sympathomimetics, modafinil, opioid analgesics, histaminergic, antihistaminergic, cholinergic, anticholinergics, dopaminergic, or antidopaminergic drugs; and antihypertensive treatment with alpha agonist effect in the last 48 h.

Other exclusion criteria were history of adverse or allergic reactions to propofol (allergy to soy or any other component of it), alcohol or drug abuse, and a full stomach. Withdrawal criteria were patients with any adverse event during induction such as excitation, hypotension with a

mean arterial pressure drop over 20%, bradycardia < 40 beats per minute, and nausea. After applying all mentioned criteria and checking the usability of the collected data we had 23 raw EEGs with a minimum length of 100 min. Our study population showed a wide range of levels of education. While some patients only had 5 years of education, others received a master's degree. The data collection period was from October 2021 until December 2022 with a goal to have groups of similar size with at least 10 patients.

2.1 Intervention procedure

The patients were randomly assigned to two groups:

Group 1 Propofol-remifentanil anesthesia.
Group 2 Dexmedetomidine-propofol-remifentanil anesthesia.

Once admitted to the surgical ward, the patient was monitored in a standard way with non-invasive blood pressure (PANI), pulse oximetry, electrocardiography, capnography and frontal raw and processed EEG (SEDLine, Masimo, Irvine, Ca, USA). Further, an intravenous catheter was placed and connected to an infusion system. EEG was recorded perioperatively. Before anesthesia induction, we recorded 90 s of EEG during eyes-closed and eyes-open conditions.

2.2 Anesthetic protocols

2.2.1 Group 1: Propofol-remifentanil anesthesia

TCI Propofol Induction (Schnider Model) with the Primea Orchestra Infusion pump (Fresenius-Kabi, Bad Homburg, Germany) in training mode was initiated at 8 mg/kg/h until unresponsiveness (LoR, loss of responsiveness to call and to moderate shoulder touch). Following LoR, we changed to the TCI mode to keep the effect site (Ce) calculated at time to LoR. In consideration of previous data on a possible overdosage of propofol with the Schnider model during induction phase, we reduced the Ce by 15% of the Ce at LoR. [32, 33]. After assessing the state of clinical unconsciousness/unresponsiveness we proceeded to intubate the patient after starting a TCI pump with remifentanil (4.5 ng/ml, Minto PKPD model) and administering rocuronium (0.6 mg/kg) [34]. Propofol was dynamically adjusted to maintain a visible alpha band similar to the one observed at LoR and a spectral edge frequency (SEF) 95 as displayed on the SEDLine monitor at a minimum value of 10 Hz. Remifentanil was adjusted with a hemodynamic response of 15% increase in heart rate or mean arterial pressure. The end of the propofol infusion was recorded as well as patient recovery time, measured as time to react to name calling (RoR). At propofol-stop, remifentanil was reduced to an effect-site concentration of 3 ng/ml until extubation.

2.2.2 Group 2: Dexmedetomidine with minimal propofol anesthesia

An intravenous infusion of dexmedetomidine began with the Primea Orchestra infusion pump at 0.8 µg/kg/h. To mitigate potential side effects, such as hypertension and bradycardia, and in line with recommendations from the pharmacokinetic model of Hannivoort [35], bolus doses of dexmedetomidine were not used. After 10 min, a propofol infusion with a target Ce of 2.0 ug/ml was started. Remifentanil was started and set to an effect-site of 4.5 ng/ml. Rocuronium (0.6 mg/kg) was administered for intubation. After intubation, propofol was reduced to 0.5 µg/ml and dynamically adjusted to maintain a SEF > 8 Hz for the remaining time of the surgery. This group had a lower SEF threshold as dexmedetomidine is known to induce strong slow wave activity, independent of its capacity to produce unconsciousness [31]. At propofol-stop remifentanil was reduced to 3.0 ng/ml effect-site. Remifentanil and dexmedetomidine infusions were stopped at extubation time.

No patient received preoperative premedication. In both groups, systolic blood pressure, cardiac frequency, pulse oximetry, capnography, and SEDLine EEG were monitored throughout the surgical procedure and for at least one hour post-operatively. Multimodal analgesia and a morphine dose of 0.05–0.1 mg/kg body weight were delivered 30 min prior the end of surgery at discretion of the anesthetist in charge. No drugs such as ketamine, midazolam, atropine, or other anticholinergics were used at any time. The Ce of propofol was registered during all the cases. In cases where BMI > 30, the dose was weight-adjusted [36]. Haemodynamics were supported with volume, ephedrine, or phenylephrine depending on the clinical judgement of the attending anesthesiologist. Target blood pressure was in a range of 15% from pre-anesthesia blood pressure.

2.3 Cognitive assessment

Cognitive assessments were performed with the MoCA test in the validated Chilean version before and one hour after RoR [37]. We evaluated the postoperative level in the PACU by applying a sedation agitation scale 10 min, 30 min, and 60 min after RoR [38]. As there are no validated tests to assess emergence delirium in the elderly, we used the Spanish version of the MoCa test to detect pre- and postoperative cognitive status changes in the PACU. We did not intend to assess for a POCD with a later onset. It has been shown that collecting tests results is most reliable when done one hour after extubation as it

avoids direct effects of decreasing anesthetic drug blood levels [10]. Patient cooperativeness was assessed with the sedation agitation scale.

Figure 1 presents the patient collective, types of surgeries, and timelines of the anesthesia protocols of both groups.

2.4 EEG recording and pre-processing

The EEG was recorded with the SEDLine monitor (Masimo Corporation, Irvine, CA) at sample rates of 178 or 89 Hz using the standard EEG electrode strips attached to the patient's forehead (a 4-channel frontal montage F7-Fp1-Fp2-F8, a reference electrode at AFz and ground electrode at Fpz). For analysis, we unified the sample rate to 89 Hz after applying a 30 Hz low-pass filter. Because of the amplitude issue of the SEDLine, we did not process the absolute amplitude information [39]. EEG data was exported via USB using the *data export* function and the trend data was retrieved via USB drive from the SEDLine monitor and using the software Masimo Instrument Configuration tool (MICT).

From the raw EEG, we calculated the power spectral density (PSD) and the density spectral array (DSA) using the *pwelch* function in MATLAB (R2022a). The frequency resolution was 0.35 Hz. For the more dynamic induction and emergence periods, we used a segment length of 5 s with a 2 s shift to calculate the DSA. During maintenance, EEG we calculated the DSA with a segment length of 10 s with an 8 s shift. For burst suppression patterns we visually assessed the raw EEG.

2.5 Statistical analysis

Because of the small sample size, we used non-parametric approaches and effect sizes with 95% confidence intervals to present our data. A power analysis for EEG analysis was not conducted and our results are based on the data available. For pairwise comparisons we used the Mann–Whitney *U* test (MATLAB, *ranksum*) and the Chi-squared test (https://www.socscistatistics.com/tests/chisquare2/default2.aspx) to check for differences in sex distribution. The significance level was set to $p < 0.05$. To compare the EEG features we used the *area under the receiver operating characteristic* (AUC) with 10 k-fold bootstrapped 95% confidence intervals as described in the measures of effect size (MES) toolbox [40]. If the confidence interval does not contain AUC = 0.5, the result can be considered significant on a $p < 0.05$ level. To correct for multiple comparisons, we discuss results only as significant if the difference occurs in neighboring frequencies (PSD) or clusters (AUC). These approaches have previously been published [16, 41–43].

3 Results

3.1 Patient demographics

There were no significant differences in the demographic factors between the two groups. Patients in the dexmedetomidine-propofol group received significantly less propofol and had a significantly lower SEF at LoR than the patients in the propofol group. The detailed values are presented in Table 1.

3.2 Cognitive evaluation

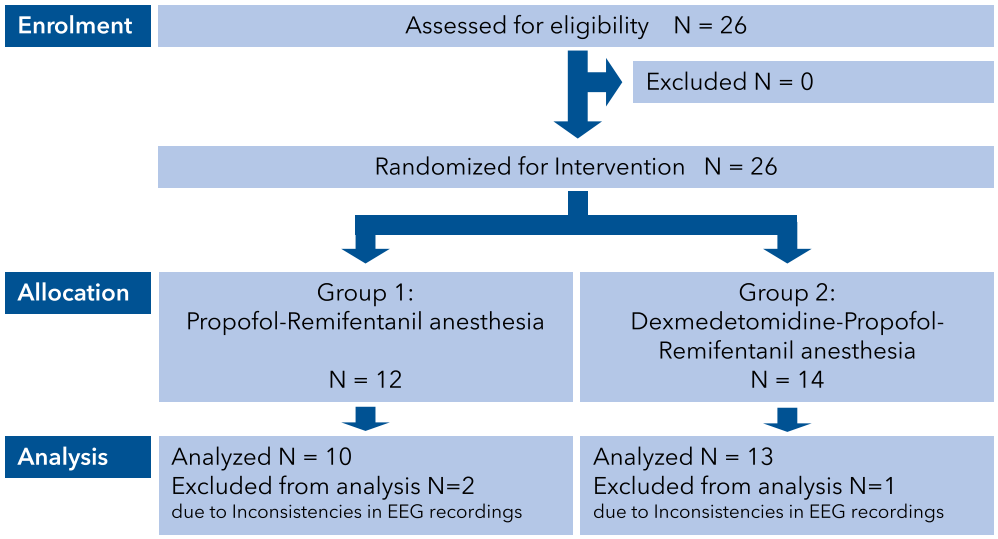
Comparing the results of the pre- and post-surgery MoCa tests, we found no significant differences between the groups. In the whole study collective, we could not find one individual patient with a significantly decreased MoCa score in the PACU. The results of the sedation agitation scale revealed that all patients were calm and cooperative and had no symptoms of sedation surplus at 10 min, 30 min, nor 60 min after RoR. Despite patients in the dexmedetomidine group experiencing longer durations of anesthesia and consequently receiving a higher dosage of anesthetic, there were no observed reductions in sedation agitation scale nor MoCa scores one hour post-surgery. Hence, in our patients, the total given amount of dexmedetomidine and/or propofol does not have an impact on the cognitive performance one hour after surgery.

3.3 Electroencephalographic patterns

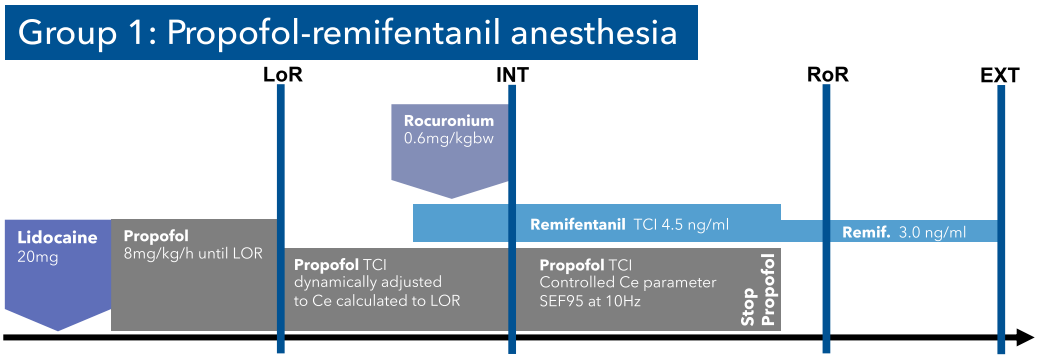
As presented in Table 1, we found significant differences in the processed EEG parameter SEF, validating the different titration approach. The more detailed analysis of the spectral EEG characteristics over time also showed significant differences between the two groups. When dividing the observations by clinical time points, we found the following differences:

3.3.1 During the induction period

There were no significant differences between the groups at baseline, as shown in Fig. 2A. Three minutes into the delivery of the first drug, i.e., propofol in the propofol-only group and dexmedetomidine in the dexmedetomidine and propofol group, we found significant differences between the EEG under dexmedetomidine and under propofol (Fig. 2B). At LoR these differences were even more pronounced (Fig. 2C). In the dexmedetomidine group LoR occurred significantly faster after starting propofol TCI



Types of surgery	
Orthopedic surgery	8 (4/4)
Vascular surgery	2(1/1)
Abdominal surgery	11(3/8)
Genitourinary surgery	2(1/1)
Gynecologic surgery	2(2/0)



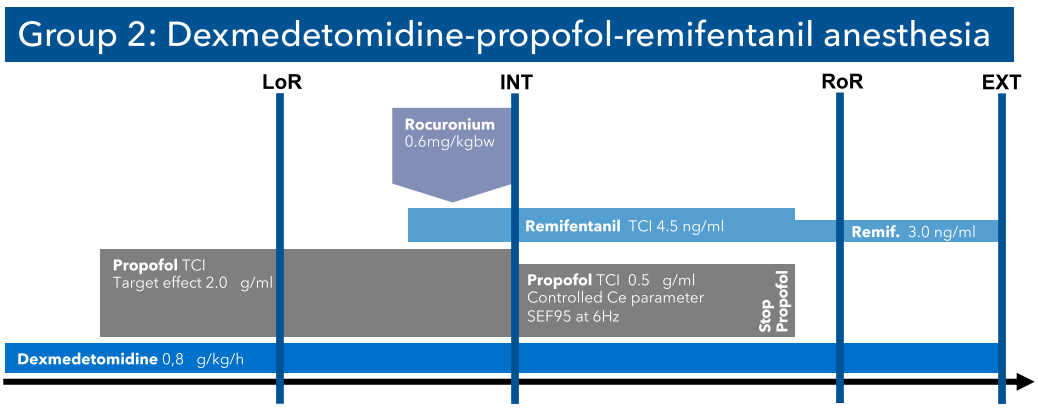


Fig. 1 Patient collective and timeline showing the protocol of drug delivery for the two anesthetic regimens. Top: Patient collective and types of surgery. Middle: For the patients receiving a slow propofol induction; Bottom: For the patients receiving a slow propofol induction after starting a continuous infusion of dexmedetomidine. Own representation of the CONSORT-Diagram [65]

Table 1 Patient demographics and group specific parameters. Median [range] BMI: body mass index; MoCa Montreal Cognitive assessment, Ce calculated effect site concentration, LoR loss of response, RoR recovery of response, PSI patient state index (Sedline), SEF spectral edge frequency 95

	Propofol (n = 10) Median [range]	Propofol + Dexmedetomidin (n = 13) Median [range]	P-value	Effect size AUC [95%CI]
Age [year]	74.5 [71–83]	82 [70–93]	0.1199	0.70 [0.47–0.78]
Gender female/male	8/2	6/7	0.1917	
BMI [kg/m^2]	27.27 [17.57–35.38]	24.91 [18.73–31.22]	0.2512	0.35 [0.12–0.61]
MoCa pre/post	22.5/22.5 [17–27/17–27]	21.0/20.5 [6–26/5–25]	0.0789/0.0543	–
Sedation-agitation-scale	4-4-4	4-4-4	0.5	–
Study level [years of education]	5.6 [2–12]	5.58 [0–12]	0.8024	0.53 [0.30–0.78]
ASA	2.5 [2, 3]	3 [2, 3]	0.3791	–
Start Propofol to LoR time [min]	9 [6–12]	2 [0–5]	< 0.0001	0.0 [0.0–0.0]
Ce Propofol at LoR [µg/ml]	2.65 [1.9–3.3]	2.0 [2–2]	0.0004	0.1 [0.0-.3]
Ce Propofol Maintenance [µg/ml]	1.9 [1.2–2.3]	0.5 [0.3–1.3]	< 0.0001	0.02 [0.0-.05]
Ce Propofol at RoR [µg/ml]	0.5 [0.4–4.5]	0.2 [0.1–0.4]	< 0.0001	0.01 [0.0-.05]
Delta CeP LoR vs. CeP RoR	2.10 [-2–2.9]	1.80 [1.6–1.9]	0.1486	0.3 [0.07–0.56]
Stop Propofol to RoR time [min]	13 [2–22]	17 [7–33]	0.3518	0.62 [0.37–0.84]
Duration anesthesia [min]	175 [100–267]	176 [101–456]	0.5765	0.57 [0.32–0.81]
PSI at LoR	74 [54–88]	83 [25–92]	0.2901	–
SEF at LoR [Hz]	20.5 [10–26]	10 [2–20]	0.0011	0.1 [0.01–0.24]

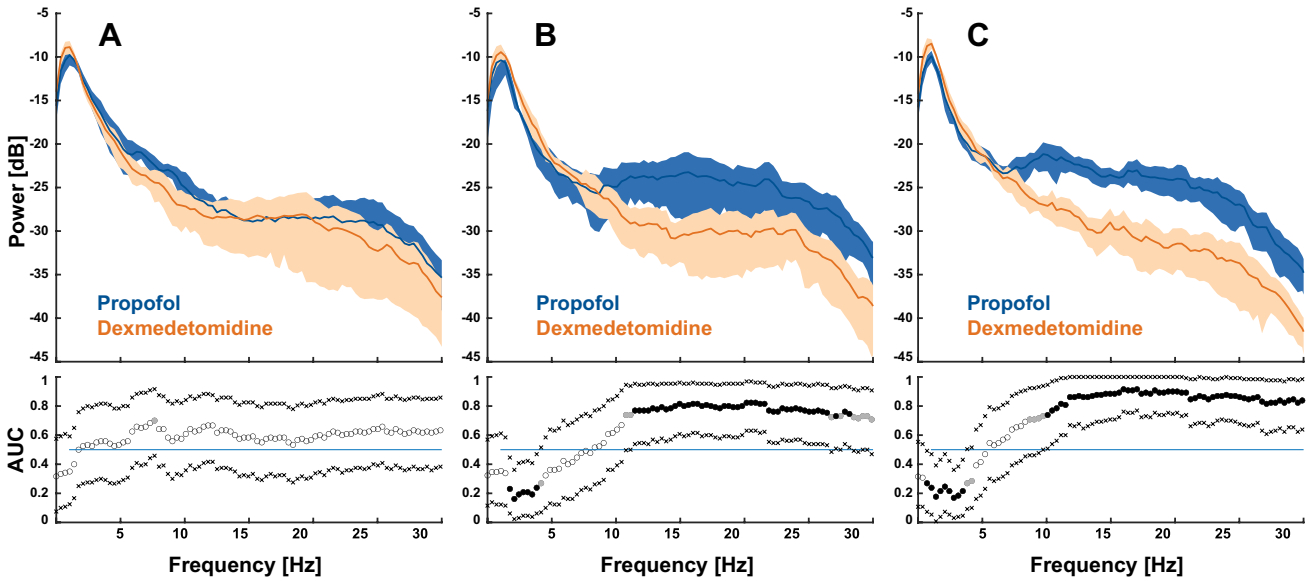


Fig. 2 Power spectral density plots (PSD) comparing the patient from the propofol and dexmedetomidine-propofol group at different time points. **A** Before the delivery of any drug there were no significant differences in the PSD between groups. **B** 3 min after starting dexmedetomidine or propofol infusion, the propofol group showed significantly stronger power in alpha- and beta-frequencies and significantly less power in the delta range. **C** At loss of responsiveness (LoR) the patients in the propofol group, that on average received propofol for around 10 min, showed significantly higher power in the alpha-band and beta band and significantly less power in the delta-band than the patients in the propofol-dexmedetomidine group that had received propofol for 2 min on average. The AUC plots indicated the calculated AUC value ('o') and the 95% confidence intervals ('x'). Filled circles indicate a significant difference defined by the confidence interval not containing AUC = 0.5

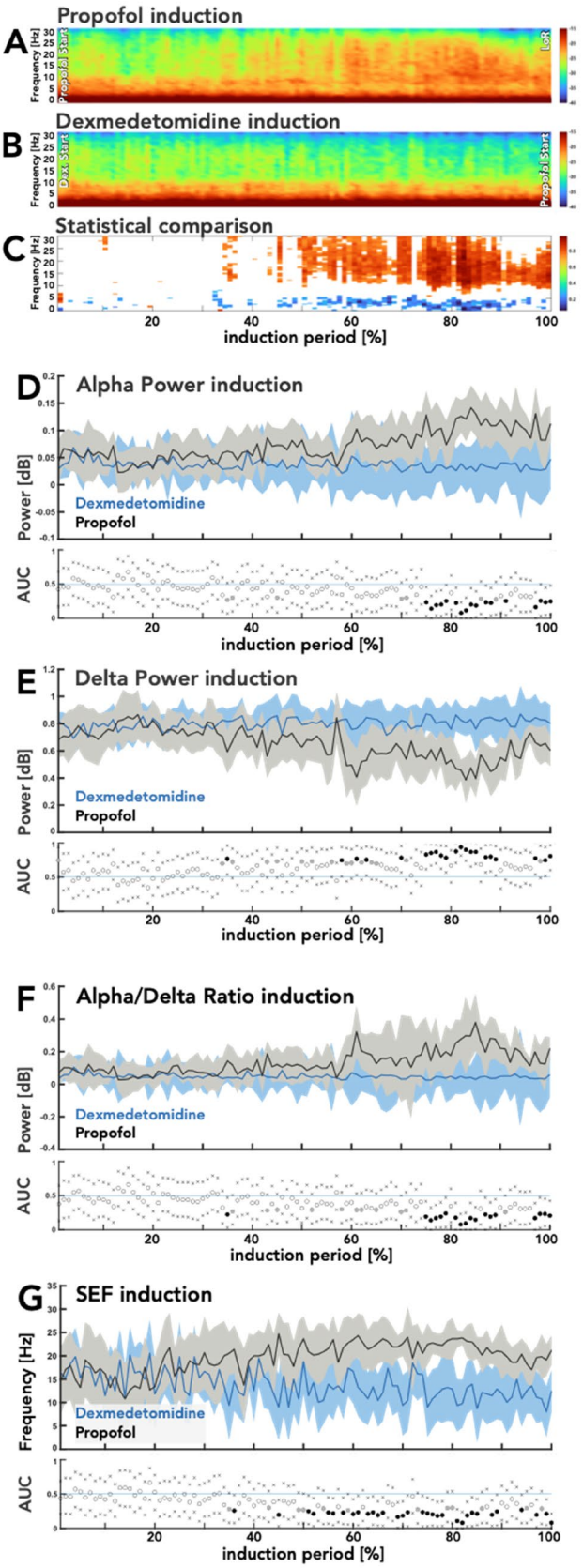


Fig. 3 Group-level density spectral arrays (DSA) showing the course of the spectral power during the initial drug infusion. To account for the risk of comparing wake rhythms with deeper sleep rhythms, we have normalized the induction time to 100%. **A** Group-level DSA for the episode of the start of propofol infusion to the loss of responsiveness (LoR). In median it took 9 [6–12] minutes from propofol start until LoR. At around 40% an activation of beta-frequencies could be observed. **B** Group-level DSA for the episode from the start of the dexmedetomidine infusion to the start of the propofol infusion. The time was exactly 10 min, but for comparison the time was normalized to 100%. A slight decrease of relative power in the higher frequencies could be observed over time. **C** Statistical comparison of the two groups. Starting around 35% the power in the higher (beta-band frequencies) was significantly higher in the propofol group and the relative power in the delta-band was significantly lower. Red color indicates a significantly higher power in the propofol group and blue a significantly higher power in the propofol dexmedetomidine group. **D** The relative alpha band power began to significantly differ after around 75% of the induction period. **E** The relative delta band power began to significantly differ after around 75% of the induction period. **F** The alpha to delta ratio began to significantly differ after around 75% of the induction period. **G** The SEF began to significantly differ after around 50% of the induction period

(2 min [0–5]) than in the propofol-only group. (9 min [6–12]).

When comparing the spectral features of propofol and dexmedetomidine longitudinally, we observed the previously described beta-band activation in the propofol group (Fig. 3A) which was not seen when the patient received dexmedetomidine (Fig. 3B) [25]. The comparison of the substance-specific differences revealed significantly higher relative beta-band power and significantly lower relative delta-band power in the propofol group (Fig. 3C).

3.3.2 During anesthesia maintenance

The differences observed between propofol and dexmedetomidine at LoR persisted throughout anesthesia maintenance. Strong delta oscillatory activity and activity in alpha-band were observed in both groups (Fig. 4A, B). When comparing the DSA of both groups, the EEG in the propofol-dexmedetomidine group had significantly more relative power in the delta-band frequencies and significantly less power in the higher frequencies, including alpha band frequencies most of the time (Fig. 4C).

3.3.3 During the emergence period

The substance-specific differences between the groups persisted throughout emergence. Only shortly before RoR did the EEG patterns start to overlap.

Figure 5 presents the detailed results.

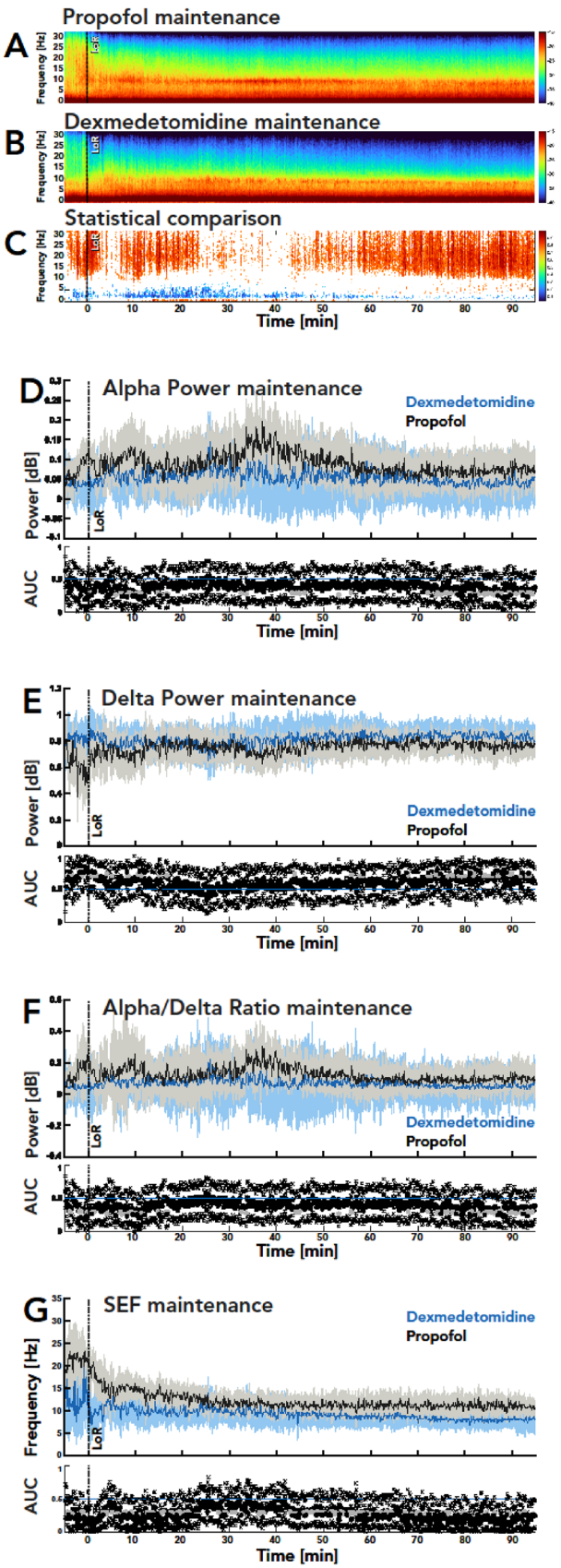


Fig. 4 Group-level density spectral arrays (DSA) showing the course of the spectral power from 5 min before LoR to 95 min into surgery. **A** The patients in the propofol group showed the "rail-pattern" typical for that substance. Around LoR the fading of the beta-activation could be observed. **B** Patients that received dexmedetomidine and propofol also showed the slowing of the EEG around LoR and a delta-dominant pattern with some alpha-band activity throughout the 95 min. **C** Statistical comparison of the two groups. The power in the higher (beta-band frequencies) was significantly higher in the propofol group and the relative power in the delta-band was significantly lower. Red color indicates a significantly higher power in the propofol group and blue a significantly higher power in the propofol dexmedetomidine group. **D** The relative alpha band power during maintenance only showed significant differences around LoR and the beginning of the maintenance period. **E** The relative delta band power during maintenance only showed significant differences around LoR. **F** The alpha to delta ratio during maintenance only showed significant differences around LoR and the beginning of the maintenance period. **G** The SEF was significantly lower for the dexmedetomidine and propofol group for most of the maintenance period

4 Discussion

This study evaluated perioperative EEG and postoperative cognitive outcomes following propofol-remifentanil TCI with and without dexmedetomidine in a cohort of patients aged 70 years or older. The two regimens did not differ in terms of recovery times nor postoperative cognitive outcomes as evaluated by the sedation agitation scale and MoCa test, respectively. Besides the significantly lower propofol concentration in patients receiving dexmedetomidine, we also found very different spectral EEG characteristics between the groups. Patients receiving dexmedetomidine and propofol showed significantly lower power in the alpha- and beta-band than patients receiving only propofol. Thus, despite their different EEG patterns, both anesthetic regimens allow for proper anesthesia navigation in the elderly without leading to worsened cognitive outcomes.

The typical "rail pattern" for propofol with dominant oscillatory activity of the delta and alpha band frequencies of the EEG at LoR previously described in young patients was also observed in our old patients [26, 44]. We attribute this finding to our slow induction protocol that may allow the aged brain to smoothly transition into the "rail pattern" EEG as well. The age-induced decrease in EEG alpha-band power observed in older patients under propofol or sevoflurane anesthesia has been widely described as a predictor of burst suppression [16, 42, 45–47]. Most of these studies use a propofol bolus, TCI effect site EC 50–95% targeting, or fast induction to represent "real world practice" showing a high risk (up to 70% in patients over 70 years) of developing burst suppression [45]. To overcome this issue, we looked for new strategies to prevent overdosing in elderly patients. Our strategy was to use a slow induction to induce strong alpha oscillatory activity and to prevent the development of EEG burst suppression as previously shown in a study with

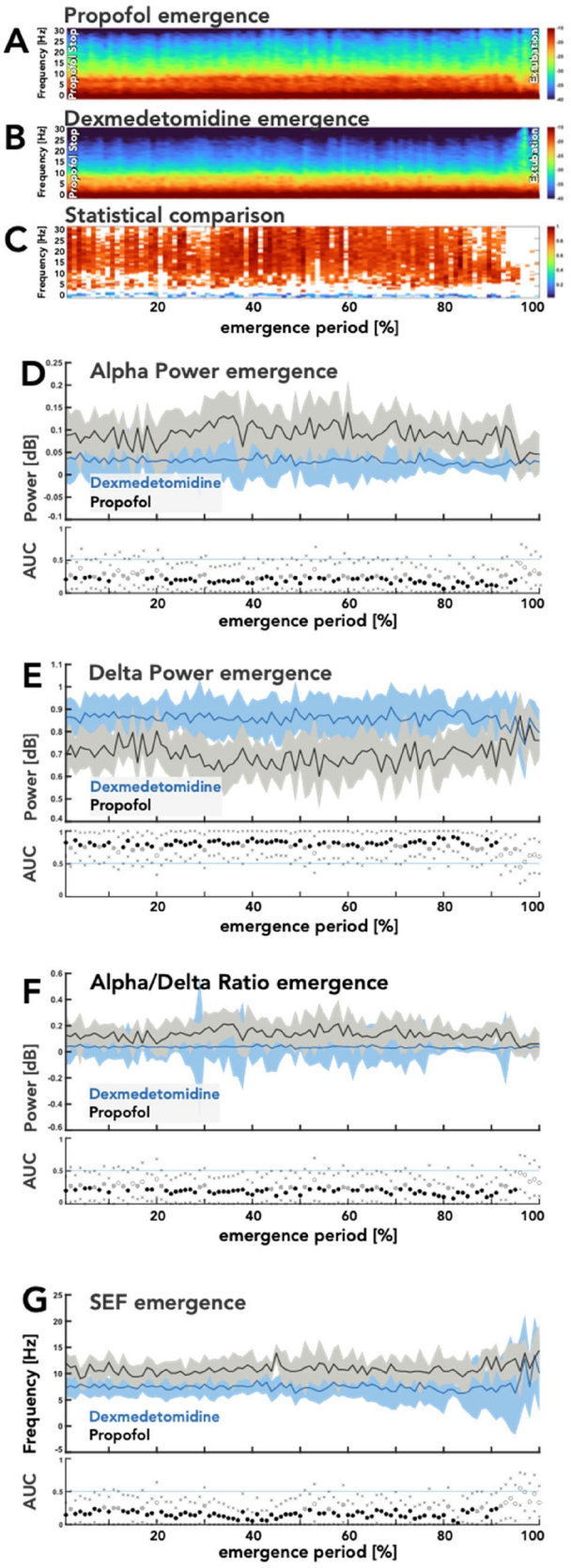


Fig. 5 Group-level density spectral arrays (DSA) showing the course of the spectral power during anesthesia emergence. To avoid comparison of EEG patterns from awake patients with those that are still at the beginning of emergence the time was normalized to 100% for each patient. **A** The patients in the propofol group changed from dominant activity in the delta-band and alpha-band to a dominance in the higher frequencies. **B** Patients that received dexmedetomidine and propofol changed from dominant activity mainly in the delta-band dominance in the higher frequencies. **C** Statistical comparison of the two groups. The power in almost all frequencies was significantly higher in the propofol group. At the end of emergence there were no significant differences between the groups. **D** The relative alpha band power was significantly higher in the propofol group for most of the emergence period. **E** The relative delta band power was significantly lower in the propofol group for most of the emergence period. **F** The alpha to delta ratio was significantly higher in the propofol group for most of the emergence period. **G** The SEF was significantly higher in the propofol group for most of the emergence period

younger patients [26]. The smoother transition into unconsciousness facilitates a more tailored propofol titration, thus better aligning with individual requirements. Unlike most studies in elderly patients, we did not observe burst suppression at any time in either group. This may have contributed to the positive cognitive outcomes observed as burst suppression is thought to be a risk factor for a neurocognitive dysfunction in elderly patients [15–18, 45].

It has been established that strong alpha power represents a favorable EEG pattern [15, 16, 41, 47]. Slow titration of propofol until LoR facilitates these favorable EEG patterns and may help pharmacodynamic navigation during maintenance. Taking the cortical dynamics of the aged brain into account might help to compensate for the flaws of the established PK models.

A slow or stepwise propofol induction could potentially diminish impacts on the brainstem, reduce hemodynamic side effects, and yield more localized effects of the drug targeting cortico-cortical or thalamo-cortical connectivity. From a pharmacological point of view, slow induction produces a more homogeneous mixing and less dissociation of the plasma concentration with the effect site concentration, thereby reducing the models' overprediction [48, 49].

The second strategy implemented in this study was to reduce propofol consumption, and thus its anticholinergic impact, by taking advantage of its synergistic effect with dexmedetomidine [50–53]. Dexmedetomidine is a drug with more than 20 years of use in ICU and anesthesia in some countries. It has been associated with a decrease in the frequency of delirium [54–56].

While previous reports have documented the decreased propofol requirement when combined with dexmedetomidine, this has not been studied throughout the whole course of anesthesia in major surgeries with elderly patients. Xiong et al. reported a reduction of the Ce of propofol at LoR of around 30% when combining it with a Ce of 0.8 ng/ml of dexmedetomidine in young patients;

however, no EEG was recorded [57]. Another study also reported lower propofol requirement in combination with dexmedetomidine during BIS index-guided closed-loop anesthesia. Additionally, this study showed a significantly higher index in the propofol-only group [58]. This difference is in line with our observations. A multi-channel EEG study revealed drug-specific differences between dexmedetomidine and propofol in a concentration-dependent manner [59, 60]. None of these studies were conducted in the elderly. With our findings, we could fill this knowledge gap.

Both drugs have different modes of action to induce sedation or anesthesia (disconnected consciousness and/or unconsciousness). Propofol primarily acts through the gamma aminobutyric acid (GABA) pathway and receptor-triggered activity, causing decreases in cholinergic activity and cortico-cortical uncoupling resulting in the inhibition of information integration [61]. On the other hand, dexmedetomidine mediates its effect through presynaptic alpha-2 (α2)-adrenergic receptors located in the locus coeruleus, thereby blocking the release of norepinephrine to higher structures and reducing its activating effect [62]. This presents an indirect mechanism to reduce arousal and slow brain activity as observed in the EEG. Using dexmedetomidine with propofol exploits dexmedetomidine-induced reduction of noradrenergic signaling while concomitantly reducing anticholinergic effect of propofol. This could be particularly useful in vulnerable patients because it could lead to a faster wash out which in turn could help restore the ability to integrate information in this narrow functional reserve space. So, the difference in perioperative EEG signatures may be attributed to the different anesthetic mechanisms. While we observed the typical alpha and delta pattern for propofol, the slow delta-band activity dominated in the dexmedetomidine and propofol group. This may suggest that the alpha band power may only act as predictor of cognitive impairment in the context of an exclusively GABAergic regimen. By stopping dexmedetomidine and remifentanil at extubation we tried to lower the amount of "incoming data" to the awakening brain. It also helps to lower coughing reflex and rises tube tolerance. The avoidance of an information-integration imbalance in aged and vulnerable brain could mitigate the risk of emergence delirium.

The observation that despite the slow and finely titrated induction in the propofol group, the need to reduce the effect-site concentration of propofol during anesthesia (only identifiable by EEG) was probably a reflection of the recently described multi-stable oscillation dynamics of the brain. This tendency to oscillate towards slower states, and eventually cause EEG markers such as alpha-oscillatory activity disappear, would require constant monitoring and adjustment of drug administration. This tendency is probably more pronounced in aging brains [63].

4.1 Limitations

The main limitation of our study is the small sample size. We tried to address this limitation by applying non-parametric statistical tests and using effect sizes to appropriately present the results. Of course, further studies should be conducted to confirm the validity of our results in a more heterogeneous patient cohort, particularly considering the gender imbalance in our data. Additionally, our patients were part of a high-risk population but were not tested for frailty itself. Many had a low level of education and limited access to health care and pre-habilitation. This collective is not comparable to patients coming from developed countries. Further, a more sophisticated cognitive assessment protocol covering a longer time period should be applied in future to evaluate the impact of the anesthesia regimen on the cognitive trajectory. Despite the usefulness of the MoCA test for cognitive assessment, limitations such as educational level, language, and customs have been described [64]. In this study, the test was carried out with the validated adjustments for the Chilean population, which has especially low levels of education [37]. Due to the rurality of southern Chile, low baseline MoCA values were observed in our patient collective, but this value was not decreased in postoperative evaluation.

The EEG was recorded with a SEDLine monitor and due to technical issues affecting the EEG amplitudes, we only used relative power for our analyses [39]. In the future, multichannel EEG setups without this issue could facilitate a more detailed analysis of the EEG. We did not include hemodynamic parameters in our study data, but they should be included in future studies.

Dexmedetomidine not only has anesthetic-sparing effects, but also reduces the use of opioids, blunts the sympatholytic stress response, and decreases neuroinflammation. However, to evaluate all these effects a larger patient collective with a multifactorial analytic approach would be needed. While postoperative delirium occurring following PACU discharge was not evaluated in the present study, this type of cognitive dysfunction is etiologically diverse. A broad range of factors not directly related with the orderly reconnection process after anesthesia—sleep disturbances, sleep apnea, neuroinflammation, isolation, pain, etc.—may better account for such disorders.

5 Conclusion

In conclusion, this pilot study shows that the two anesthesia regimens used did not lead to a significant difference in the immediate postoperative cognitive outcome. Both regimens avoided abnormal electroencephalographic patterns, specifically burst suppression induced by anesthetic overdose. The fact that the two techniques present different conditions in

the EEG without differing cognitive outcomes raises the question whether alpha band power per se is a valid predictor of frailty or is that only in the case of GABAergic anesthetics. The results also underline the importance of interpreting the perioperative EEG correctly in the context of the applied anesthetic regimen. Further, we show the value of using a slow anesthesia induction with EEG monitoring in the anesthetic management of aged and vulnerable patients.

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Data availability If there is interest in the raw data we collected, please write an email to Pablo O. Sepúlveda ().

Declarations

Competing interests Dominik M. Mehler, Luis F. Cardenas, Ignacio Barra, Fernando Zurita, Francisco Lobo and Pablo O. Sepúlveda state that neither has a competing interest of financial or personal nature. Matthias Kreuzer is named as inventor for a patent recently filed on a method for intraoperative EEG monitoring: US Patent App. 17/717,708, 2022.Matthias Kreuzer, David P. Obert, and Gerhard Schneider are named as inventors for a patent recently filed on a novel method for intraoperative EEG monitoring: US Patent App. 17/728,310, 2022.

Ethical approval We conducted the study with the approval of the research ethics committee of the Universidad Austral de Valdivia and it was registered in Clinical Trials under the number NCT05425069.

Consent to participate All patients sighed the declaration of consent to be part of this study.

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