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Citation: Windmann, Victoria et al. "Influence of midazolam premedication on intraoperative EEG signatures in elderly patients." Clinical Neurophysiology 130, 9 (September 2019): 1673-1681 © 2019 International Federation of Clinical Neurophysiology

As Published: http://dx.doi.org/10.1016/j.clinph.2019.05.035

Publisher: Elsevier BV

Persistent URL: https://hdl.handle.net/1721.1/125942

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Influence of midazolam premedication on intraoperative EEG signatures in elderly patients☆

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☆The study was performed at the Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Berlin, Germany.

Abstract

Objective

To investigate the influence of midazolam premedication on the EEG-spectrum before and during general anesthesia in elderly patients.

Methods

Patients aged ≥65 years, undergoing elective surgery were included in this prospective observational study. A continuous pre- and intraoperative frontal EEG was recorded in patients who received premedication with midazolam (Mid, n = 15) and patients who did not (noMid, n = 30). Absolute power within the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–25 Hz) frequency-bands was analyzed in EEG-sections before (pre-induction), and after induction of anesthesia with propofol (post-induction), as well as during general anesthesia with either propofol or volatile-anesthetics (intra-operative).

Results

Pre-induction, α-power of Mid patients was lower compared with noMid-patients (α-power: Mid: −10.75 dB vs. noMid: −9.20 dB; p = 0.036). After induction of anesthesia Mid-patients displayed a stronger increase of frontal α-power resulting in higher absolute α-power at post-induction state, (α-power: Mid −3.56 dB vs. noMid: −6.69 dB; p = 0.004), which remained higher intraoperatively (α-power: Mid: −2.12 dB vs. noMid: −6.10 dB; p = 0.024).

Conclusion

Midazolam premedication alters the intraoperative EEG-spectrum in elderly patients.

Significance

This finding provides further evidence for the role of GABAergic activation in the induction of elevated, frontal α-power during general anesthesia.

Trial Registry Number

NCT02265263. 23 September 2014. Principal investigator: Prof. Dr. med. Claudia Spies. (https://clinicaltrials.gov/ct2/show/NCT02265263).

Keywords: Premedication; Benzodiazepines – midazolam; EEG; Geriatric anesthesia; Propofol anesthesia

1 Introduction

The benzodiazepine midazolam is routinely used as premedication before anesthesia to reduce anxiety and agitation. However, its influence on EEG signatures at induction of anesthesia is still unknown.

These EEG signatures are increasingly studied to monitor the brain-state of patients under general anesthesia (Purdon et al., 2015b). New insights within this field will hopefully help to improve anesthesia monitoring and management based on a deeper understanding of its neurophysiological background (Purdon et al., 2015b).

Especially in elderly patients, the use of benzodiazepines is currently under debate, as they are associated with adverse neurological outcomes after surgery (Pisani et al., 2009; Radtke et al., 2010). Midazolam acts as a positive allosteric modulator at the gamma aminobutyric acid A receptor ($GABA_A$)-receptor (Greenblatt et al., 1989). This GABAergic effect causes sedation, however, at low doses benzodiazepines can lead to a paradoxical excitation – patients present with agitation and anxiety. In the EEG, benzodiazepines cause an increase of power within the beta-(β) frequency band (12–25 Hz) and decreased activity in the alpha-(α) band (8–12 Hz) (Greenblatt et al., 1989; Borgeat et al., 1997; Gugino et al., 2001).

Different to midazolam, propofol (2,6 di-isopropyl-phenol), a frequently used anesthetic agent, acts as a direct $GABA_A$ agonist (Bai et al., 1999; Downing et al., 2005; Campo-Soria et al., 2006). Propofol-induced unconsciousness is characterized by an increase of delta-(δ) power (0.5–4 Hz) and the appearance of highly coherent frontal α-power (Gugino et al., 2001; Feshchenko et al., 2004; Cimenser et al., 2011; Purdon et al., 2013; Akeju et al., 2014; Akeju et al., 2016; Hight et al., 2017). This increase of frontal α-power is thought to be mediated by GABA-induced thalamo-cortical feedback mechanisms (Ching et al., 2010). In elderly patients, the activation of frontal α-power during anesthesia has been reported to decrease with higher age and an additional cognitive decline (Purdon et al., 2015a; Chiang et al., 2011; Giattino et al., 2017).

Even though both midazolam and propofol act at the $GABA_A$-receptor, they occupy different binding sites of receptor and have been shown to act synergistically in combination, as lower doses of propofol are needed to induce unconsciousness when midazolam is administered as well (Wilder-Smith et al., 2001).

However, a detailed understanding of the dynamics following $GABA_A$-receptor pre-activation before induction of general anesthesia and the related EEG signatures is scarce (John et al., 2001; Alkire et al., 2008; Palanca et al., 2009).

This study aims to investigate the influence of midazolam and propofol on the intraoperative EEG spectrum in elderly patients. We hypothesize that a co-activation of the $GABA_A$-receptor by both midazolam and propofol augments the increase of frontal α-power during general anesthesia.

2 Methods

2.1 Patient population

This prospective, observational cohort study was performed as a subproject of the BioCog Study at the university hospital Charité – Universitätsmedizin Berlin Campus Charité Mitte and Campus Virchow-Klinikum, Germany (NCT02265263). Ethics approval was obtained from the institutional review board (EA2/092/14). While inclusion of patients for the BioCog study took place from October 2014 until April 2017, patients for this subproject were examined between February 2015 and April 2017 after written informed consent from each patient was obtained. Intraoperative EEG measurements were performed at the study center Charité – Universitätsmedizin Berlin.

Patients were eligible if they were aged 65 years or older, undergoing elective surgery under general anesthesia with an expected operating time of at least 60 minutes. Exclusion criteria comprised preoperative Mini-Mental-State-Examination (MMSE) < 24 points, neuropsychiatric morbidity that limited conduction of neurocognitive testing, and proposed neurological surgery, maxillofacial surgery or surgery in prone position were not included, as an abundance of EEG artefacts could be expected.

Patients receiving oral premedication with midazolam prior to induction (Mid group) were compared to an age-matched group of patients not receiving oral premedication (noMid group). Dosage and time of administration

(30 min prior to induction) were determined according to the standard operating procedures at Charité - University hospital. Patients with i.v. application of midazolam before induction of anesthesia were excluded from further analyses.

Baseline demographic data, including neurological preconditions, patient history, other comorbidities, and long-term medication, were obtained on the day of inclusion by reviewing the medical records. MMSE, measurement of hand grip strength (HGS) and Timed up and Go Test (TUG), and Charlson Comorbidity Index (CCI) were performed preoperatively (Podsiadlo et al., 1991; Charlson et al., 1987).

Furthermore, patients were asked to fill out the EQ-5D-5L questionnaire that assesses quality of life (Herdman et al., 2011). We analyzed the item concerning anxiety and depression, as anxiety is associated with lower α-power and might confound our results (Siciliani et al., 1975).

Medication and dosage for induction of anesthesia were not part of the study protocol and chosen according to clinical needs and determined by the anesthetist in charge. Analgesia (remifentanil or fentanyl) and neuromuscular blocking drugs (rocuronium, cis-atracurium, mivacurium or succinylcholine) were administered during the induction period and maintenance of anesthesia according to clinical needs.

2.2 Data collection and EEG analysis

A continuous pre- and intraoperative frontal EEG was recorded with the Sedline Brain Function Monitor (Masimo Corporation, Irvine, California) starting before induction of anesthesia and lasting throughout the entire surgery. Following skin preparation with alcohol, electrodes were placed on the patients' forehead according to the standard Sedline electrode array at Fp1, Fp2, F7 and F8, with earth electrode at Fpz and reference electrode 1 cm posterior to Fpz in the midline. Electrode impedance was kept below 5 kΩ for each electrode. The EEG data were obtained with a sampling rate of 250 Hz. During the pre-induction recording patients were asked to keep their eyes closed.

In a post-hoc approach we also analyzed baseline EEGs recorded on the day before surgery, when patients were free of any midazolam or propofol medication, in order to assess the validity of our results. The EEGs were recorded using a 10/20 electrode montage with reference electrode on the mastoid bone. Only the frontal channels (Fp1/2 and F7/8) were considered for further analyses.

For EEG pre-processing bandpass filters (0.5–40 Hz) were applied to the raw EEG. Subsequently, the EEGs were inspected visually and 10-second artefact-free time windows were selected manually from the period before induction of anesthesia (pre-induction) and from a period after administration of the hypnotic propofol (post-induction), as well as 30 minutes after induction representing a stable intra-operative state (intra-operative). This period was determined by taking the first artefact-free window without any signs of burst suppression at least 2 minutes after propofol administration by an investigator blinded to whether premedication was given or not and under supervision by a neurologist (S.K.), who is trained in neurophysiology and EEG analysis.

EEG spectral analysis was computed with the Chronux Toolbox (Bokil et al., 2010) for Matlab (The MathWorks, Inc., Natick, Massachusetts, United States) by using a custom written Matlab code (Copyright 2015 The General Hospital Corporation, authored by Seong-Eun Kim, Ph.D.) in dependence on Cornelissen and colleagues (Cornelissen et al., 2015). We calculated a pooled electrode that equally weighted the signals recorded from Fp1, Fp2, F7, and F8 to obtain estimates of frontal power spectra. Power spectra quantifying the energy in the EEG at each frequency were calculated by using a multitaper method with 2-second time windows with 1.9 s overlap, time–bandwidth product TW = 3, number of tapers K = 5, and spectral resolution of 2 W = 3 Hz. The resulting data were transformed to a decibel scale. $[Power\,(dB) = 10log10\,(Power(\mu V))]$.

Group-level spectrograms displaying the power at different frequencies over time were computed by taking the median across patients.

2.3 Statistical analysis

The present study was principally intended as an exploratory pilot study. As this is a subproject of a bigger study, patients were included according to the sample size calculation for the BioCog study. The underlying statistical hypothesis (association between Midazolam premedication and perioperative α-band) has been generated from the descriptive analyses, the subsequent statistical tests are therefore only to be understood as exploratory ones.

Patients were divided into age-matched groups to account for the age-dependency of the intraoperative EEG spectrum (Purdon et al., 2013). For each patient receiving premedication with midazolam, two control patients without premedication were selected. There was no one-to-one but only group level matching. Accordingly, a difference in age (±2 years) was allowed if the average age in both groups remained similar.

The mean absolute power within the α-band (8–12 Hz) in the Mid and noMid group at post-induction state represented the primary outcome variable. Secondary outcome parameters comprised the power from 0.5 to 4 Hz for delta (δ), 4–8 Hz for theta (θ) and 12–25 Hz for β-band power in each group.

Numerical calculations were performed with SPSS, Version 24 (Copyright SPSS, Inc., Chicago, IL 60606, USA) and a custom-written Matlab code (MathWorks Inc.). Significance was calculated by using the Mann-Whitney-U-Test for independent variables and Wilcoxon-Signed-Rank test for dependent samples. We computed the 95% CI of the median difference at each frequency to assess statistical significance for the difference of power spectra within

different frequency bands by using a frequency domain-based bootstrapping algorithm (n = 500) resampling the Fourier coefficients (Kirch, 2011, Cornelissen et al., 2015). Values were considered significant only if the 95% CI did not contain 0 for consecutive frequencies ≥2 W within the individual frequency bands.

In bivariate correlations, we analyzed an association between patient characteristics (age, anesthetic agent, preoperative MMSE, CCI) and frontal α-power. Additionally, multiple linear logistic regression analysis was calculated for possible confounding variables (age, anesthetic agent, preoperative MMSE, CCI, and midazolam) on frontal α-power.

For nominal data, statistical analysis was performed with Chi-square test from Pearson. Data are expressed as mean with standard deviation, median with interquartile range or as frequencies (%). Values were considered significant if $p < 0.05$. No corrections for multiple comparisons were made.

3 Results

A total of 70 raw-EEGs were recorded and manually inspected for artefacts and noise in this study. We excluded patients who were improperly fitted with EEG electrodes resulting in poor data quality, recordings with spectral artefacts (n = 6), and EEGs without a pre-induction recording (n = 5). Furthermore, patients who received midazolam intravenously immediately before induction of anesthesia during the pre-induction EEG recording, were not included in the analysis, as the shorter mode of action could have biased our results. (n = 2). Additionally, patients receiving a hypnotic other than propofol for anesthesia induction were excluded from analyses for this study (n = 4). Of the remaining 53 patients, 15 were premedicated with midazolam and 30 patients with similar age were selected to represent the control group, resulting in a total of 45 age-matched patients included in the final analysis (Mid: mean age 71 years (±3.57) vs. noMid: mean age 71 years (±3.80)). Fig. 1 shows the study consort diagram.

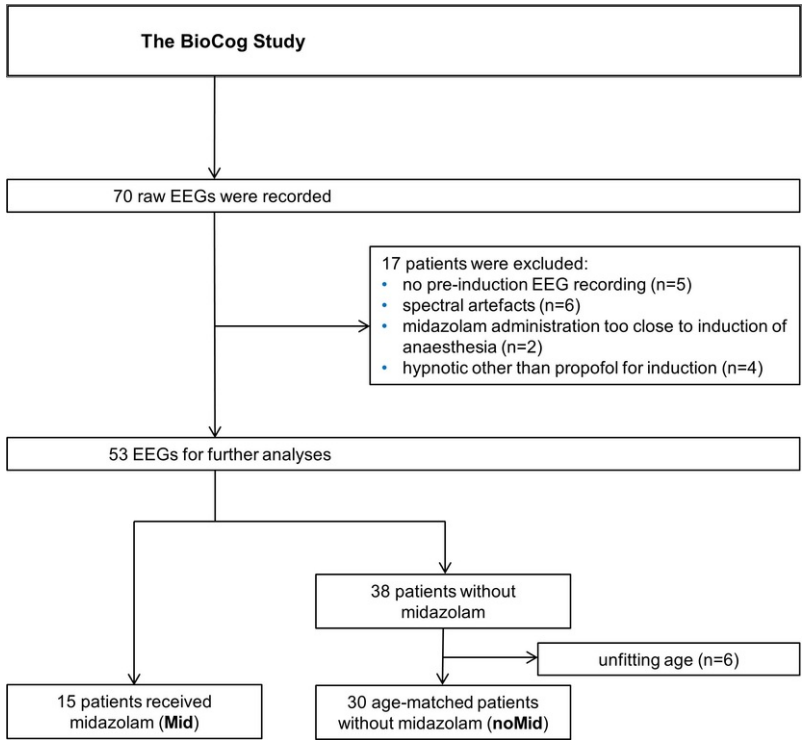

Fig. 1 Study consort diagram.

3.1 Patient characteristics

Patients receiving premedication with midazolam presented with a trend towards lower doses of propofol per kg body weight for induction of anesthesia. Anesthesia was maintained either intravenously with propofol (n = 15) or with volatile anesthetics (sevoflurane (n = 23) or desflurane (n = 7)). Intraoperatively administered analgesics comprised fentanyl (n = 28) and/or remifentanil (n = 18). We observed no significant dose-differences between Mid- and

noMid-patients (Table 1).

Table 1 Baseline **c**haracteristics of patients with (Mid) and without premedication (noMid). Data are presented as mean (SD), median [IQR], or as number (proportion). A p-value <0.05 is significant.

	NoMid (n = 30)	Mid (n = 15)	p-value
Age (years)	71 (4.05)	71 (3.57)	0.837
Female sex (%)	46.7	46.7	>0.999
BMI (kg m^{-2})	26.63 (3.37)	26.49 (3.67)	0.819
ASA I/II/III (n)	2 (2–3 [2–3]) 0/23/10	2 (2–2 [1–3]) 1/12/2	0.239
MMSE	29 (28–30 [27–30])	29 (28–30 [24–30])	0.140
HGS dominant hand (kg)	30.75 (10.33)	26.67 (9.61)	0.588
TUG (s)	8 (6–9 [4–15])	9 (8–11 [4–13])	0.106
Charlson Comorbidity Index	0 (0–1 [0–3])	0 (0–2 [0–4])	0.157
Premedication with midazolam (mg kg^{-1} body weight)	–	0.07 (0.02) (n = 15)	
Type of surgery			
Abdominal %	33.33	33.33	>0.999
Cardiothoracic %	3.33	3.33	>0.999
Musculoskeletal %	63.34	63.34	>0.999
Medication for induction of anesthesia			
Propofol (mg kg^{-1} body weight)	2.53 (0.93) (n = 30)	2.16 (0.52) (n = 15)	0.159
Fentanyl (µg kg^{-1} body weight)	2.86 (0.82) (n = 20)	3.39 (1.03) (n = 10)	0.477
Remifentanil (µg min^{-1} kg^{-1} body weight)	0.19 (0.05) (n = 10)	0.22 (0.12) (n = 6)	0.611
Neuromuscular blocking drugs			
Rocuronium (mg kg^{-1} body weight)	0.52 (0.06) (n = 10)	0.55 (0.14) (n = 7)	0.333
Cisatracurium (mg kg^{-1} body weight)	0.11 (0.02) (n = 10)	0.10 (0.02) (n = 4)	0.557
Succinylcholin (mg kg^{-1} body weight)	–	1.01 (0) (n = 1)	
Mivacurium (mg kg^{-1} body weight)	–	0.22 (0.02) (n = 2)	
Drugs administered additionally			
Atropine (mg kg^{-1} body weight)	0.02 (0) (n = 1)	–	0.480
Akrinor (ml kg^{-1} body weight)	0.05	0.02	0.506

	(0.04) (n = 7)	(0.01) (n = 5)	
Noradrenaline (μg kg⁻¹ min⁻¹)	0.04 (0.02) (n = 12)	0.04 (0.01) (n = 9)	0.255
Drugs administered for maintenance of anesthesia			
Propofol (mg kg⁻¹ body weight min⁻¹)*	5.65 (0.94) (n = 11)	6.33 (0.71) (n = 4)	0.441
Sevoflurane (et Vol%)*	1.53 (0.31) (n = 14)	1.56 (0.13) (n = 9)	0.877
Desflurane (et Vol%)*	4.80 (0.86) (n = 5)	5.17 (1.19) (n = 2)	0.786
Fentanyl (μg kg⁻¹ body weight)**	3.80 (1.47) (n = 19)	3.09 (0.67) (n = 9)	0.349
Remifentanil (mg kg⁻¹ body weight min⁻¹)*	0.15 (0.07) (n = 10)	0.19 (0.09) (n = 8)	0.211

* Mean rate during the intra-operative EEG segment.

** Cumulative dose administered until the end of the intra-operative EEG segment.

Patient characteristics are summarized in Table 1.

None of the patients included in this study had received benzodiazepines as part of their long-term medication prior to being admitted to the hospital. Three patients in the noMid group had suffered a TIA or apoplexia, however, they did not have any residuals impairing mobility or speech. There was no significant difference in level of anxiety and depression between both groups stated within the EQ-5D-5L questionnaire. No differences in ASA score, MMSE, GDS, HGS, TUG or CCI were observed preoperatively between the two groups. In multiple linear regression analysis, no correlation between age, preoperative MMSE, CCI and midazolam administration was observed.

3.2 Baseline EEG

At baseline, power within the α-band was not significantly different between Mid (n = 11) and noMid patients (n = 19) (Mid: 6.07 [5.20–7.62] dB vs. noMid 5.12 [1.04–12.02] dB; p = 0.230, 95% CI of the difference: −1.31 to 4.04).

3.3 Pre-Induction EEG

The pre-induction EEG revealed significantly lower α-power in the Mid group prior to induction of anesthesia (Mid: −10.75 [−13.12 to −9.39] dB vs. noMid: −9.20 [−10.94 to −7.25] dB; p = 0.036; 95%CI of the difference: −4.24 to −0.27) (Figs. 2–4). Midazolam was the only independent variable significantly associated with pre-induction α-power (p = 0.020) (Table 2).

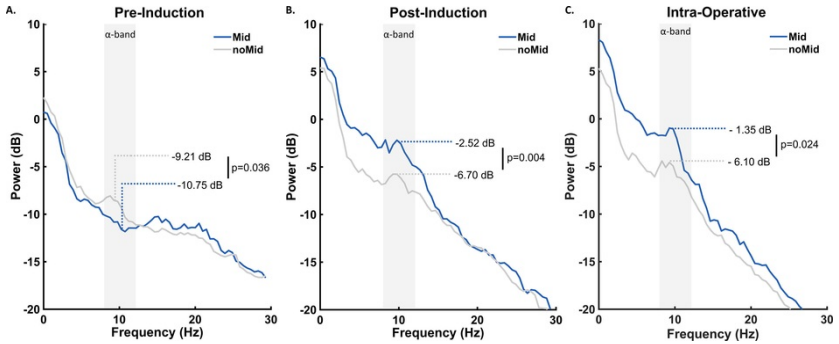

Fig. 2 Median spectra of Mid (blue) and noMid (grey) patients at Pre-induction (A), Post-Induction (B) and Intra-Operative state (C). Power (dB) is represented by the blue (Mid) and grey (noMid) line. At pre-induction state power within the α-band (8–12 Hz) is significantly lower in the Mid-Group. Mid patients show significantly higher α-power post-induction of anesthesia and intra-operatively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

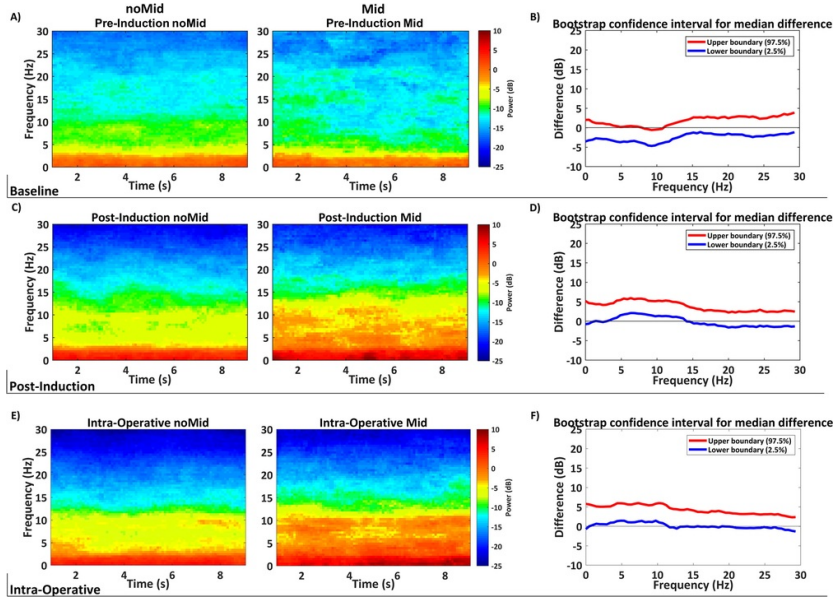

Fig. 3 Spectrograms and Bootstrap confidence interval for median differences of power in Mid and noMid patients Pre-induction (A, B), Post-Induction (C, D) and Intra-Operative state (E, F). In the spectrograms time (s) is arranged along the x-axis and frequencies (Hz) are arranged along the y-axis. Pre-induction power within the α-band (8–12 Hz) is significantly lower in Mid patients compared to noMid patients. After induction of anesthesia, power within the δ- (0–4 Hz), θ- (4–8 Hz) and α-band increases in all patients. Mid patients present with significantly higher power within the α-band.

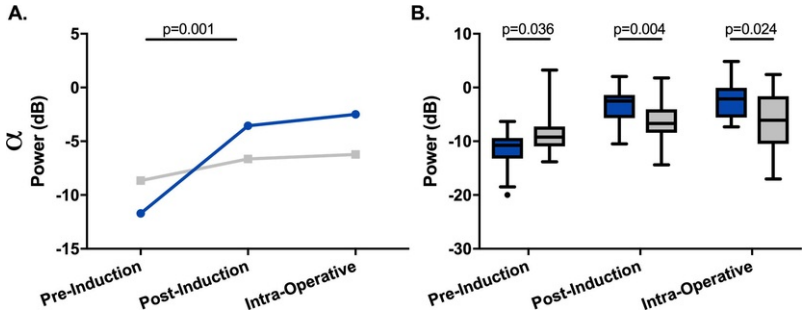

Fig. 4 Dynamics of α-power from Pre- to Post-Induction and Intra-Operative state in Mid (blue) and noMid (grey) patients. (A) The graphs show the change of power within different frequency bands at pre- and at post-induction state. The increase of frontal α-power from Pre- to Post-Induction was significantly stronger in Mid patients. (B) Boxplots depicting power within the α-band at Pre-Induction, Post-Induction and Intra-Operative state. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

Table 2 Predictors of α-power in multiple regression analysis.

Independent variables	Beta	p-value
Pre-induction α-power		
Age (years)*	−0.182	0.245
MMSE**	0.037	0.808
Charlson Comorbidity Index**	0.102	0.510
Midazolam***	−0.369	0.020

Post-induction α-power		
Age (years)*	0.017	0.912
Dose of propofol for induction (mg kg^{-1})*	−0.046	0.769
MMSE**	0.123	0.427
Midazolam***	0.390	0.017
Intra-operative α-power		
Age (years)*	−0.328	0.019
Narcotic for maintenance of anesthesia***	0.397	0.005
MMSE**	0.022	0.816
Midazolam***	0.318	0.022

* Continuous variable.

** Ordinal variable.

*** Categorical variable.

Pre-induction, no significant difference in β- θ- or δ-power between both groups was observed (see Supplementary Material).

3.4 Post-induction EEG

In the post-induction EEG, frontal α-power increased in all patients compared to pre-induction state. However, Mid patients presented with a distinctly higher frontal α-power at post-induction state compared to the spectrum of noMid patients (Mid −3.56 [−5.70 to −1.38] dB vs. noMid: −6.69 [−8.44 to −4.05] dB; p = 0.004; 95%CI of the difference: 1.34–5.22) (Figs. 2–4). Midazolam was the only significant predictor of post-induction α-power in multiple linear regression analysis (p = 0.017) (Table 2).

β-power did not differ significantly between both groups. δ- and Θ-power increased in all patients compared to the pre-induction state. Θ-power was significantly higher in Mid patients (see Supplementary Material).

Mid patients revealed a greater increase of α-power from pre- to post-induction state compared to noMid patients. The ratio of post-induction over pre-induction α-power (post-induction/pre-induction ratio) was significantly greater for Mid patients (Mid 8.60 [5.06–11.31] dB vs. noMid: 2.02 [0.26–5.68] dB; p = 0.001) (Fig. 4).

3.5 Intra-operative EEG

The intra-operative EEG was similar to the post-induction EEG. Mid patients presented with higher α-power compared to noMid patients (Mid: −2.12 (−5.60 to −0.51] dB vs. noMid: −6.10 [−10.49 to −1.60] dB, p = 0.024, 95%CI of the difference: 0.95–5.35) (Figs. 2–4). θ-, δ- and β-power were also higher in Mid patients in the intra-operative EEG-segment (see Supplementary Material).

Intra-operative α-power was correlated with midazolam application (categorical variable), the anesthetic agent administered during maintenance of anesthesia (categorical variable: propofol, sevoflurane or desflurane) and age (years). In a multivariate logistic regression including midazolam application (categorical variable), age (years), anesthetic agents administered for maintenance (categorical variable: propofol, sevoflurane or desflurane), and preoperative MMSE, only age, anesthetic agent and midazolam application remained as independent predictors for intra-operative α-power ($R^2 = 0.36$, p = 0.002) (Table 2).

4 Discussion

Intraoperative frontal α-power was increased following oral midazolam. Following administration of propofol for induction of anesthesia, our patients revealed significantly higher frontal α-power if receiving oral premedication with midazolam compared to patients without premedication. During maintenance of anesthesia α-power remained higher in premedicated patients. This finding supports our hypothesis that allosteric $GABA_A$-receptor pre-activation with midazolam facilitates induction of anesthesia, by supporting a coherent, frontal α-power at loss of consciousness (Gugino et al., 2001; Feshchenko et al., 2004; Cimenser et al., 2011; Purdon et al., 2013).

4.1 Pre-induction EEG spectrum and the influence of oral midazolam premedication

Oral premedication with midazolam causing slight sedation and relieve from anxiety caused a “paradoxical excitation” in the pre-induction EEG recordings represented by a decrease of α-power and a trend towards higher β-power in the EEG spectrum. This is in line with data of previous studies, which found that GABAergic agents such as midazolam, or low dose anesthetic agents such as propofol or volatile anesthetics cause this “paradoxical excitation” – an increase in EEG oscillation frequency in spite of sedation and drowsiness in patients (Greenblatt et al., 1989; Veselis et al., 1991; Borgeat et al., 1997; Feshchenko et al., 1997; Gugino et al., 2001; Feshchenko et al., 2004). A mathematical model published by McCarthy et al. (2008), proposes that an interaction between synaptic $GABA_A$ currents and intrinsic slow potassium currents is responsible for this excitation. These currents are thought to put post-synaptic neurons into a more excited state resulting in the generation of β-frequency anti-synchrony between reciprocally connected cortical interneurons and consequently, causing pyramidal cells to pattern their spiking behavior according to the interneuron β-rhythm (McCarthy et al., 2008).

4.2 Intraoperative EEG spectrum and the influence of oral midazolam premedication

After induction of general anesthesia with propofol, a high dose $GABA_A$ agonist, we observed an increase of frontal α-power, θ-power and δ-power in all patients, which is in line with data from the literature (Purdon et al., 2013). It has been observed that with higher, anesthetic doses of propofol, GABA-mediated post-synaptic inhibition dominates and a frontal α-rhythm is induced (Feshchenko et al., 2004; Purdon et al., 2013). This coherent, frontal α-power in the EEG spectrum is associated with a stable unconscious state and an adequate depth of anesthesia (Purdon et al., 2013; Purdon et al., 2015b). A mathematical model investigating the pathophysiology of this phenomenon stresses the role of GABAergic transmission triggering a thalamo-cortical feedback mechanisms leading to cortical synchrony, and hence, creating the coherent α-rhythm (Ching et al., 2010). Our data are in accordance with this model and support the association between GABAergic activation and the appearance of frontal α-power after induction of anesthesia, as $GABA_A$-receptor modulation in form of administration of midazolam prior to induction of anesthesia caused more pronounced α-band power.

Intra-operative frontal α-power decreases with increasing age (Purdon et al., 2015a). Maintenance of general anesthesia with volatile-anesthetics provokes slightly higher coherent, frontal α-band power compared to propofol anesthesia (Purdon et al., 2015a). These findings are in line with our data, as we found a correlation between intra-operative α-power and age and anesthetic agents, however, we were able to show that premedication with midazolam is associated with higher intra-operative frontal α-power as well.

4.3 Propofol and midazolam syngery

Even though both propofol and midazolam primarily potentiate $GABA_A$ evoked currents, they act at differing binding sites of the receptor. Midazolam predominantly binds at the α/γ-interface causing a positive allosteric modulation by increasing the binding affinity for GABA (Pritchett et al., 1989; Walters et al., 2000; Berezhnoy et al., 2004). Propofol binds at the β-subunit of the $GABA_A$-receptor, increasing not only the channel opening frequency and binding affinity for GABA, but also directly activating the receptor even in the absence of endogenic GABA (Hales et al., 1991; Hara et al., 1993; Jurd et al., 2003). It has been shown in embryonic hippocampal neurons of mice that benzodiazepines and propofol act synergistically on the $GABA_A$ receptor. When administered in combination, they showed a higher potency than expected from potency of the additive effect of each drug (McAdam et al., 1998). In our study cohort, premedicated patients showed a trend towards lower doses of propofol needed for induction of anesthesia, compared to patients without premedication. This observation is in line with data gathered in previous trials, which found that after premedication with benzodiazepines such as midazolam, reduced doses of propofol for induction of anesthesia were needed to cause unconsciousness (Short et al., 1991; Martlew et al., 1996; Olmos et al., 2000; Wilder-Smith et al., 2001). We were able to show that propofol and midazolam also have a synergistic effect on the EEG spectrum under general anesthesia, as the intra-operative frontal α-power was significantly higher if both drugs were administered. Their synergy on anesthetic endpoints such as hypnosis has been previously attributed to their different binding sites on the $GABA_A$-receptor (Hendrickx et al., 2008). As midazolam is a positive allosteric modulator of the $GABA_A$-receptor, the observed interaction between midazolam and propofol may also be due to a potentiation of the affinity of the receptor to the direct agonist propofol (Fig. 5). We propose that the increased, intraoperative frontal α-power in the Mid-group is related to an allosteric modulation of the $GABA_A$ receptor, which facilitates the GABAergic effect of propofol during induction and maintenance of anesthesia. Consequently, our data give further evidence for a role of GABA-mediated feedback mechanisms in the generation of frontal α-power under general anesthesia.

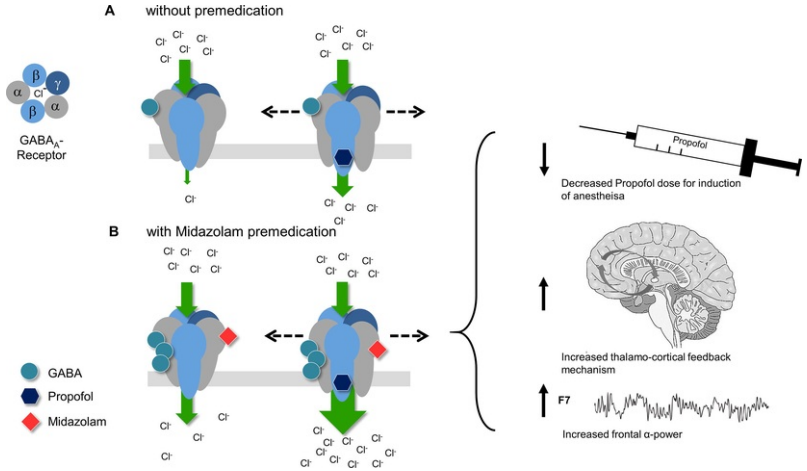

Fig. 5 Synergistic action of propofol and midazolam at the $GABA_A$-receptor. (A) Propofol induces allosteric activation of the $GABA_A$ receptor inducing Cl^- influx. (B) After oral premedication with Midazolam (triggers GABA affinity at the $GABA_A$ receptor) propofol acts synergistically on the $GABA_A$ receptor leading to a further increase of Cl^- conductance (B). This synergistic activation leads to a reduced dosage of propofol needed for anesthesia induction, a higher intraoperative EEG frontal α-band power which most likely is induced by an increased thalamo-cortical feedback mechanisms.

4.4 Limitations

Since our data were collected within the framework of an observational trial during routine care of patients, drug administration and anesthesia management was not performed in a controlled way. This may have biased our results, although no significant differences in drug dosages of opioids and muscle relaxants between both groups were observed.

Furthermore, midazolam was not administered randomly but according to clinical needs. Benzodiazepines are associated with adverse outcomes especially in elderly patients with lower neurocognitive function or mild dementia and are consequently prescribed more reluctantly in patients with these conditions (Adodra et al., 1995; Pisani et al., 2009; Radtke et al., 2010). Consequently, patients presenting with these conditions may have been more likely to not receive midazolam. This may have confounded our results. However, preoperative ASA-score, MMSE, HGS, TUG, and CCI did not differ between both groups or correlated with administration of midazolam or α-power. Thus, we hypothesize that both groups had a similar state of health, and had a comparable preoperative neurocognitive status and perioperative risk. Nevertheless, we were not able to suspend this confounder entirely within the framework of this observational trial and it may have skewed our results. In accordance to the observational character of this study the noMid group was not given a placebo. Consequently, we cannot rule out certain effects of anticipation.

The Sedline EEG Neuromonitor is one of the leading neuromonitors on the market to date and the standard monitor used in our clinic. The aligned EEG sensor is provided by Masimo. This array has a built-in frontal reference. However, as the region of interest in this study was frontal as well, a reference placed on the mastoid might have yielded even stronger results. Only the baseline EEG recordings used a mastoid reference. Power during these recordings was notably higher in all patients compared to pre- and post-induction and intra-operative EEG measurements. This can most likely be attributed to the different position of the reference electrode during these recordings.

Furthermore, our data are limited with respect to the small sample size, as only 15 patients received midazolam preoperatively in our cohort. This is related to the general clinical recommendation for anesthesiologists to limit administration of benzodiazepines in elderly patients, as premedication with benzodiazepine is suspected to increase the risk of developing postoperative delirium (Pisani et al., 2009; Radtke et al., 2010). As our study focused on patients aged >65 years, and EEG signatures are highly associated with age, the observations cannot be applied to all ages (Purdon et al., 2015a). Consequently, larger randomized controlled trials are needed to confirm our findings.

4.5 Conclusions

This study reveals a significantly stronger activation of frontal α-power in response to induction and maintenance of anesthesia in patients receiving premedication with midazolam. This finding provides further evidence for the role of GABAergic transmission in the appearance of coherent, frontal α-activation at “loss of consciousness” mediated by anesthetic drugs and suggests that premedication with midazolam facilitates $GABA_A$-receptor activation due to its allosteric modulation of the receptor.

Funding

The research leading to these results has received funding from European Union funded Seventh Framework research program [FP7/2007–2013], under the grant agreement No. HEALTH-F2–2014–60246, BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly), www.biocog.eu. Additional (internal) funding was obtained from the Berlin Institute of Health (BIH).

Author contributions

Conceived and designed the experiments: CS, SK, VW. Performed the experiments: VW, SK. Analyzed the data: VW, SK, EB, DK, GL. Wrote and reviewed the manuscript: VW, SK, EB, DK, GL, CS.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.05.035.

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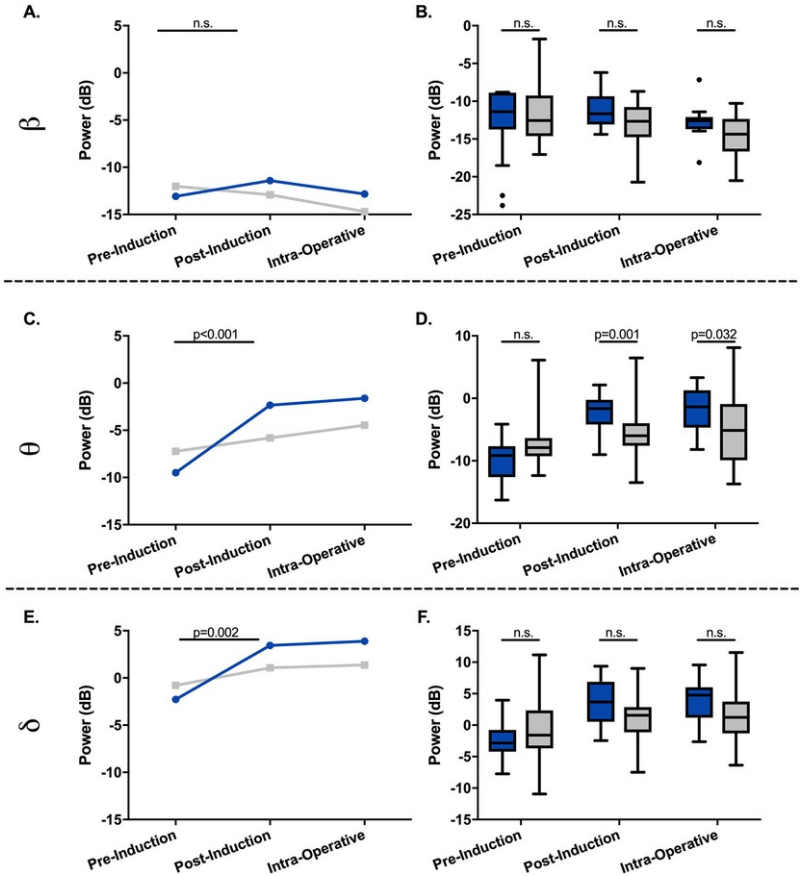
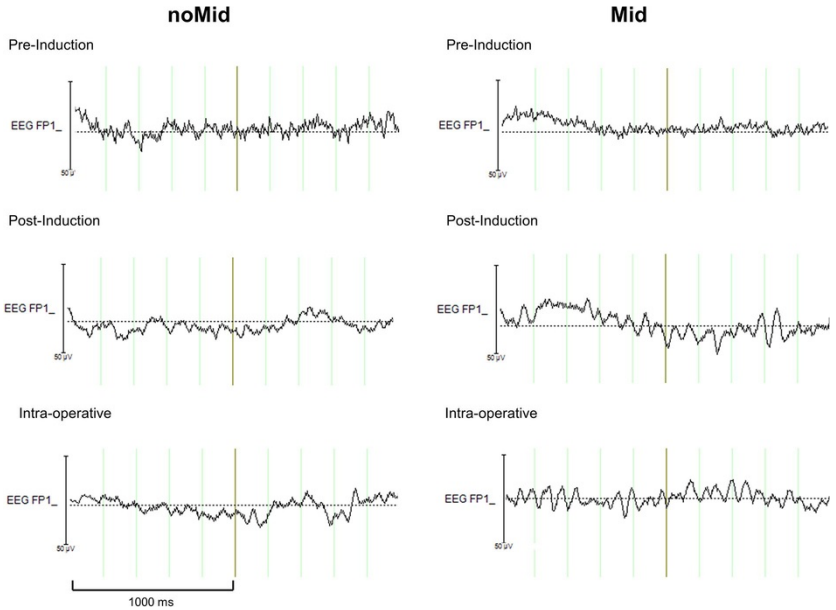
Appendix A. Supplementary material

The following are the Supplementary data to this article:



Supplementary figure 1 Dynamics of β-, θ- and δ-power power in Mid (blue) and noMid (grey) patients. Graphs (A) and (B) show the change of power from Pre- to Post-Induction and Intra-Operative state within the β-frequency band, graphs (C) and (D) within the θ-band and graphs (E) and (F) within the δ-band.



Supplementary figure 2 Raw EEG segments of patients with and without midazolam premedication (Mid and noMid patients) at Pre-, Post-induction and Intra-Operative state.

Highlights

- Frontal α-band power increases after induction of anesthesia with propofol.
- Premedication with midazolam elevates the increase of frontal α-power after administration of propofol compared to non-premedicated patients.
- α-power remains higher in premedicated patients during maintenance of anesthesia with propofol/volatile anesthetics.

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