Dexmedetomidine Induces Low Patient State Indices While Preventing the Development of Postoperative Delirium in Older Patients Undergoing General Anesthesia - A Secondary Analysis of a Randomized Controlled Trial (NEUPRODEX)

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Research Article

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Abstract

Background: Dexmedetomidine may have a delirium preventive effect in high-risk surgical patients. Accurate frontal EEG-guided anesthesia can decrease the incidence of postoperative delirium by avoiding too deep anesthesia. Aim of our study is to evaluate the incidence of postoperative delirium under intraoperative frontal EEG neuromonitoring during general anesthesia with dexmedetomidine.

Methods: A secondary analysis of a single-center, randomized, double-blinded, placebo-controlled trial. Patients > 60 years were included with either abdominal or cardiac surgery, receiving intraoperative dexmedetomidine or placebo. Delirium incidence was measured up to the fifth postoperative day. Anesthetic depth was measured as Patient State Index (PSi™) every 15 minutes during surgery using EEG-based neuromonitoring.

Results: Of the 60 patients included, the incidence of postoperative delirium was significantly reduced in the dexmedetomidine group (n=28) vs. the control group (n=32) (p=0.031). A PSi less than 25 at least once was seen in 85.2% of the verum group and 58.1% of the placebo group (p=0.024). The mean (SD) PSi value in the dexmedetomidine group was 28.17 (10.35) and 33.55 (11.31) in the placebo group using mixed-model ANOVA.

Conclusions: Intraoperative Dexmedetomidine reduces the incidence of postoperative delirium in older patients at risk, although presenting with lower intraoperative PSi levels.

Key Points

- **Question:** This secondary analysis addresses whether the perioperative coadministration of dexmedetomidine in elderly surgical patients influences the depth of anesthesia measured with the patient state index.
- **Findings:** Coadministration of dexmedetomidine in addition to routine anesthesia administration induces lower levels of EEG-based indices, indicating a deeper level of sedation besides reducing the incidence of postoperative delirium.
- **Meaning:** Although deep anesthesia is known to be associated with an increased risk of developing postoperative delirium, this was not seen in our study, where intraoperative coadministration of dexmedetomidine reduces the incidence of postoperative delirium in combination with a lower level of intraoperative EEG-based indices.

Introduction

Intraoperative frontal electroencephalographic (EEG) monitoring offers the possibility of more precise quantification of anesthetic depth and therefore allows a differentiated view of the effects of anesthetics on the brain.⁽¹⁾ Routinely used EEG neuromonitors generate anesthetic depth indices by processing raw EEG data based on an inbuilt algorithm.⁽²⁾ The calculation of these indices is based on characteristic

signatures in electrical activity related to the state of consciousness during general anesthesia and on the detection of specific EEG patterns, e.g., burst suppression patterns. Burst suppression indicates a very deep state of general anesthesia presenting an isoelectric line with intermittent EEG activity.⁽¹⁾ There is evidence that intraoperative EEG monitoring-guided anesthesia decreases the rate of postoperative delirium (POD), by avoiding prolonged phases of very deep anesthesia.^(3–5) While electroencephalography during anesthesia originally aimed to detect intraoperative awareness, in recent years, the depth of anesthesia and its possible consequences have increasingly become the focus of scientific work. In 2005, Monk and colleagues were able to show in a prospective evaluation of a population of 1,064 patients that the cumulative duration of deep anesthesia, defined as bispectral index <45, significantly increased the one-year mortality.⁽⁶⁾ Regarding this, there is growing concern that anesthetic management and even specific anesthetic agents may worsen outcomes in high-risk patients.^(7,8) Dexmedetomidine is a highly specific and selective alpha-2 adrenoreceptor agonist and shows dose-dependent sedative, analgesic and anxiolytic effects. As a sedative and anesthetic adjunct, it is increasingly used in the operating room. In the perioperative setting, several clinical studies have shown that dexmedetomidine significantly reduces the need for hypnotics and opioids.^(9–11) Since some opioids and sedatives have been shown to have prodelirigenic effects, dexmedetomidine may presumably reduce the incidence of POD through an opioid-reducing effect.⁽¹²⁾ In a large study population of over 700 patients over 65 years of age after noncardiac surgery, Su et al. were able to demonstrate that a postoperative administration of dexmedetomidine significantly reduced the incidence of POD during the first 7 days after surgery, moreover without the frequent occurrence of hypotension or bradycardia.⁽¹³⁾ With regard to EEG, specific patterns under dexmedetomidine could recently be identified^(14–18), and it was also shown that dexmedetomidine will decrease EEG-based index values. The extent to which intraoperative administration of dexmedetomidine can influence the depth of anesthesia and PSi under general anesthesia possibly through opioid-saving effects, by meanwhile reducing the risk to develop POD in elderly patients is subject of the present secondary analysis.

Methods

Study Design and Setting

Data collection in this prospective randomized, double-blind, placebo-controlled clinical trial according to the Federal Institute for Drugs and Medical Devices (BfArM) was performed between July 2014 and July 2018 and was carried out at the Charité - Universitätsmedizin Berlin. The study was approved by the Federal Institute for Drugs and Medical Devices (BfArM) on 13th September 2013 and by the Ethics Committee of the Department for Health and Social Affairs (LAGeSo, Fehrbelliner Platz 1, 10707 Berlin, Chairwoman: Dr. Mai) on 30th January 2014 (13/0491-EK 11). The study was registered in the European Register for Clinical Studies (Eudra-CT 2013-000823-15) and in the WHO Register under ClinicalTrials.gov (NCT02096068; first posted 26/03/2014).

All patients gave written informed consent obtained by a physician. The study protocol was performed in accordance with the relevant guidelines. This manuscript adheres to the applicable CONSORT guidelines as well. The datasets generated and analyzed during the current study are not publicly available due to German data law concerning clinical trials according to the Federal Institute for Drugs and Medical Devices. Primary study results have been published.⁽¹⁹⁾

Delirium monitoring was carried out using validated measurement instruments in accordance with the German S3 guidelines on Analgesia, Sedation and Delirium management in intensive care medicine. Examination for delirium during intensive care treatment was performed by a study doctor at least twice a day. POD incidence was measured with the "Confusion Assessment Method for the ICU (CAM-ICU)" or the "Confusion Assessment Method (CAM)" up to the fifth postoperative day as the primary endpoint in the original study. As a secondary endpoint, the depth of anesthesia was measured as the Patient State Index (PSi™) throughout the surgery using processive electroencephalography and electromyography (EEG/EMG) monitoring, a common form of EEG-based neuromonitoring (SedLine®).

Participants

Out of a total of 484 male and female patients being assessed for eligibility, 63 patients > 60 years were included who underwent either large abdominal surgery or elective cardiac surgery (mainly PPPD or CABG surgery). All patients had a preoperative discussion, gave their written consent and local data privacy regulations were complied with. Exclusion criteria were a known intolerance or allergy to dexmedetomidine or one of the ingredients, manifest cognitive impairment defined as "Minimal mental status examination (MMSE)" score <24, traumatic brain injury in the current history, intracranial hemorrhage within one year before enrollment, psychiatric illness, addiction history (alcohol or drug abuse), acute intoxication, hemodynamic failure at the time of randomization (severe hypotension with mean arterial blood pressure <55 mmHg despite vasopressors and optimized preload), AV block first or second degree (without pacemaker), severe bradycardia (heart rate <50/min preoperative, permanent), spinal cord injury with autonomous dysregulation, preoperative acute cerebrovascular event with neurological residuals, liver insufficiency (Child C cirrhosis, MELD score > 17), insufficient knowledge of the German language, severe hearing or visual impairment, illiteracy, the unwillingness to save and pass on pseudonymised disease data as part of the clinical trial, accommodation in an institution by judicial or official order (according to AMG §40 (1) 4), patients without permanent residence or circumstances that jeopardize availability by telephone or post for the 3-month follow-up examination, participation in another clinical trial after the German Medicinal Products Act at the time of inclusion and while participating in this clinical trial as well as employees of the Charité Universitätsmedizin (CVK/CCM).

Randomization was carried out by a biometrician in a 1:1 ratio and resulted in blocks of four patients being assigned to either the verum or placebo group. Patient recruitment determined the study's running time, which ended after a sufficient number of subjects had been included.

Administration of study medication as either verum or placebo was labeled with a pseudonym and provided by the hospital pharmacy. Investigators, clinicians and the patient were blinded to the allocation

of each patient and pseudonyms were created by the institute for biometrics. All patients received general anesthesia in accordance with the applicable standard operating procedures using propofol and sufentanil or fentanyl for the induction of anesthesia. To maintain anesthesia, the volatile anesthetics sevoflurane and desflurane or continuous administration of propofol was used. All anesthetic agents and opioids were given at clinical requirements by the anesthesiologists in charge. In the case of hypotension states during anesthesia, cafedrine/theodrenaline (Akrinor®) or norepinephrine was mostly used. Cardiac surgery patients additionally received orciprenaline, dobutamine, enoximone and nitroglycerin for hemodynamic support if necessary.

Study medication

There were two investigational study arms in this clinical trial. Depending on the randomization, verum [dexmedetomidine (Dexdor®)] or placebo [sodium chloride solution (isotonic saline solution)] was administered to the blinded patient. Study medication was dosed according to the adjusted ideal body weight (ABW) of the study patient. The preparation of the study medication was carried out by the pharmacy of Charité Universitätsmedizin Berlin. Patients received either a fixed rate of dexmedetomidine at a dosage of 0.7 µg/kg ABW/h or saline solution starting 10 minutes after the induction of anesthesia in advance of surgery. In case of hemodynamic side effects that could not be controlled by optimization of preload or administration of orciprenaline, the intraoperative dose was reduced to 0.4 µg/kg ABW/h or 0.2 µg/kg ABW/h. Thirty minutes prior to the expected end of surgery, the rate of infusion was reduced to 0.4 µg/kg ABW/h. After extubation, the infusion rate was further reduced by half every 20 minutes to achieve an RASS of -1/0. Infusion was paused for a maximum of 30 minutes if oversedation was suspected. If the patient was agitated (RASS>0), the dose was increased with 0.2 µg/kg ABW/h stepwise every 20 minutes up to a maximum of 1.4 µg/kg ABW/h. The administration of study medication was limited to a maximum of 48 hours and recorded separately in a drug accountability log and checked by the monitor.

EEG based Neuromonitoring

Intraoperative neurological monitoring was performed using Massimo SedLine (SEDline Root, Masimo, Irvine USA). Using this EEG-based procedure, the effects of anesthesia and sedation were measured by monitoring electrical brain activity to enable a more individual titration of anesthetics. Generally, it includes a quantitative EEG measurement of brain activity, which follows a predictable invariant pattern. The SedLine device uses a multivariate algorithm to determine the patient's EEG data from 4 channels and an additional reference and ground electrode and processes it to determine the Patient State Index (PSi) as a measurement of the depth of anesthesia.⁽²⁰⁾ During the intraoperative measurement, which provides information on power, frequency and phase from anterior-posterior relationships of the brain as well as coherence between bilateral brain regions, a comparison is made with the stored data records. The SedLine monitor uses artifact rejection techniques to further reduce the sensitivity to sources of electrical interference, such as electrocautery.⁽²⁰⁾ PSi corresponds to the patient's current level of sedation or anesthesia on a scale of 0 to 100, with 100 indicating that the patient is fully awake.⁽²¹⁾ The optimal range is between 25 and 50, with PSi values below 25 indicating a deep anesthetic state outside the

optimum range of sedation or anesthesia levels. PSi values reflect the loss of consciousness, arousal and waking up as well as reactions to harmful stimuli. The electrodes were established during the anesthetic preparations and the first value was recorded 10 minutes after the induction of anesthesia. The PSi values were then documented every 15 minutes throughout the entire procedure. To prevent perioperative oversedation, anesthesiologists were instructed to keep the PSi above 25 and therefore avoid burst suppression.

Statistical analysis

For sample size calculation, an incidence of 45% for POD was assumed, the intervention was predicted to reduce the incidence by ~ 10%. 80% power and an alpha error probability of 0.05 yielded a required group size of 58 patients. With an additional 5% drop-out rate, a total of 62 patients (31 each group) were needed.

All endpoints (primary and secondary) of the main study were first exploratively examined and evaluated descriptively. In particular, statistical measures such as mean and standard deviation (metrically scaled and normally distributed characteristics), median and interquartile difference (categorical and nonnormally distributed metric characteristics) or frequencies and proportions (qualitative characteristics) were determined. As part of the exploratory analysis, the structural groups (homogeneity) of the treatment groups were also checked.

Statistical analyses were conducted using SPSS 25 and R.3.5.1. The level of significance was defined in all cases to $\alpha = 5\%$ (two-sided). The number and proportion of patients with $PSi < 25$ was assessed at time 15, 30, 45, 60, 75, 90, 105 and 120 minutes of the procedure and overall. It was compared between groups using Chi² test. To assess the effect of dexmedetomidine vs. placebo on the depth of anesthesia, a mixed-model ANOVA was computed. This procedure takes within-patient correlation into account when modeling the measured PSi values. The main effects of dexmedetomidine and time were assessed, plus the interaction of time with dexmedetomidine.

Cumulative intraoperative quantities of opiates (fentanyl, sufentanil and piritramid) were compared between groups using the Mann-Whitney U test. Furthermore, the interquartile range (IQR) was specified.

Results

A total of 63 patients were recruited between July 2014 and July 2018 at two tertiary university hospitals in Berlin, Germany. Due to 3 dropouts, 60 of them, 28 patients in the dexmedetomidine group and 32 patients in the placebo group, were analyzed using the intention-to-treat approach. Processed EEG neuromonitoring was performed using SedLine on 58 of the included patients, 27 in the dexmedetomidine group and 31 in the placebo group (figure 1). Two measurement series, one in each group, were not carried out for logistical reasons.

Sociodemographic and clinical data showed no significant differences between the dexmedetomidine group and the placebo group; however, in the dexmedetomidine group, the incidence of POD was

significantly reduced (Table 1).

Table 1
Sociodemographic & Clinical characteristics of the study population

	Dexmedetomidine n=28	Placebo n=32	p-value
Age, years; mean (SD)	70.43 (7.14)	70.5 (6.23)	0.888 b)
Gender: female, n (%)	9 (32.2%)	9 (28.1%)	0.955 a)
Body Mass Index, kg/m ² ; mean (SD)	26.97 (4.93)	28.03 (4.66)	0.509 b)
ASA 1-2, n (%)	14	16	0.636 a)
ASA 3-4, n (%)	14	16	
Site of surgery, n (%):	13	16	0.823 a)
PPPD/Pancreatic Surgery	9	8	
Other intra-abdominal procedure	6	8	
Cardiac			
Beta-blocker intake; daily, n (%)	15 (52.6%)	18 (56.3%)	0.835 a)
Polypharmacy (five or more); daily, n (%)	15	21	0.342 a)
Preoperative NYHA 0, n (%)	18	16	0.394 a)
Preoperative NYHA 1-3, n (%)	10	16	
MMSE preoperative	*)	6	0.728 a)
25-27, n (%)	7	26	
28-30, n (%)	20		
Hemoglobin preoperative, g/dl; median [IQR]	12.2 (11.4; 13.1)	13.1 (11.8; 13.7)	0.216 b)
Heart rate preoperative, bpm; mean (SD)	72.96 (13.32)	72.81 (12.04)	0.923 b)
Received premedication, n (%)	24 (75,0%)	22 (78,6%)	0.851 a)
None	5 (15,6%)	3 (10,7%)	
Midazolam 3,75mg	3 (9,4%)	3 (10,7%)	
Midazolam 7,5mg			
a) Chi ² -Test			
b) Wilcoxon-Mann-Whitney-U-Test			
*) one patient declined MMSE in Dexmedetomidine Group			
**) one measurement series in each group not performed			

	Dexmedetomidine n=28	Placebo n=32	p-value
Length of anesthesia, minutes; mean (SD)	277,00 (96,25)	254,21 (135,19)	0,328 b)
Norepinephrine max, µg/kg/min; median [IQR]	0.07 (0; 0.1)	0.1 (0.1; 0.2)	0.064 b)
Severity of illness; median [IQR]	7 (5; 8.8)	6 (4.5; 8.5)	0.389 b)
SOFA, max.	49 (40; 48.2)	40 (32.8; 50.2)	0.104 b)
SAPS II, max.	19.5 (15.2; 24.2)	20 (14; 24)	0.833 b)
APAACHE, max.			
ICU Length of stay, hours; mean (SD)	129.4 (182.0)	105.5 (160.0)	0.866 b)
Length of stay in hospital, days; mean (SD)	23.5 (20.3)	21.0 (15.6)	0.807 b)
Recurrence to OR, n (%)	14 (50%)	12 (37.5%)	0.475 a)
Postoperative Delirium, n (%)	5 (17.9%)	14 (43.8%)	0.031 a)
Patient State Index < 25; Overall, n (%) **)	23 (85,2%)	18 (58,1%)	0.024 a)
a) Chi ² -Test			
b) Wilcoxon-Mann-Whitney-U-Test			
*) one patient declined MMSE in Dexmedetomidine Group			
**) one measurement series in each group not performed			

Overall, 70.7% of the patients had a PSi value less than 25 at least once during anesthesia. The incidence was 85.2% in the verum group (n=23) and 58.1% in the placebo group (n=18) (p=0.024). In addition, PSi values were examined at certain timepoints during surgery - at 15, 30, 45, 60, 75, 90, 105 and 120 minutes of the procedure. At 75, 90 and 105 minutes of the procedure, as well as from a general perspective, significantly more patients had PSi values lower than 25 in the verum group compared with the placebo group (figure 2).

Additionally, the PSi was evaluated using a mixed-model ANOVA. The mean PSi values in the dexmedetomidine group (SD) were 28.17 (10,35) and 33.55 (11.31) in the placebo group (figure 3). There were statistically significant main effects for both time (p=0.000) and group (p=0.000). Furthermore, there was no statistically significant interaction between time and group. (p=0.125).

The opiates fentanyl, sufentanil and piritramid were used intraoperatively (table 2). Opioid-saving effects of perioperative administration of dexmedetomidine cannot be shown, as the intraoperative opioid application was similar in both groups. In addition to opiate requirements, there were also no differences in the need for hypnotics in either group.

Table 2: Intraoperative anaesthetic requirements

	Dexmedetomidine (%)	Placebo (%)	p-value
Number (n) =			
Propofol induction	26	30	0.890 (a)
Fentanyl induction	20	21	0.630 (a)
Sufentanil induction	6	8	0.744 (a)
Sevoflurane induction	12	10	0.352 (a)
Desflurane induction	4	3	0.554 (a)
Propofol maintenance; TIVA	5	11	0.149 (a)
Fentanyl maintenance	21	23	0.785 (a)
Sufentanil maintenance	7	8	1.000 (a)
Sevoflurane maintenance	18	22	0.714 (a)
Desflurane maintenance	8	9	0.969 (a)
Dosage			
Induction of anaesthesia			
Propofol; initial dose; mg (IQR)	185 (150; 200)	165 (140; 200)	0.581 (b)
Fentanyl; initial dose; mg (IQR)	0.2 (0.20; 0.30)	0.2 (0.20; 0.25)	0.197 (b)
Sufentanil; initial dose, µg (IQR)	40 (25; 50)	40 (32.50; 50)	0.946 (b)
Maintenance of anaesthesia			
Propofol; total intravenous anaesthesia; mg/kg/h	6	6	(b)
Volatile anaesthetics; etVol% at timepoints			
Sevoflurane; etVol%; (IQR)			

_15min	1.5 (1.3; 1.7)	1.6 (1.4; 2.0)	0.214 (b)
_30min	1.5 (1.4; 1.6)	1.7 (1.4; 2.0)	0.101 (b)
_45min	1.5 (1.4; 1.6)	1.7 (1.5; 2.2)	0.105 (b)
_60min	1.6 (1.4; 1.7)	1.7 (1.6; 2.2)	0.069 (b)
_75min	1.6 (1.4; 1.7)	1.7 (1.5; 2.1)	0.065 (b)
_90min	1.5 (1.2; 1.6)	1.6 (2.0; 1.7)	0.530 (b)
_105min	1.2 (0.4; 1.5)	1.6 (2.0; 1.8)	0.078 (b)
_120min	1.3 (0.1; 1.6)	1.6 (0.8; 1.8)	0.461 (b)
Desflurane; etVol%; (IQR)			0.038 (b)
_15min	4.6 (3.8; 5,0)	4.9 (.,4; 5.4)	0.195 (b)
_30min	4.6 (3.7; 4,7)	4.9 (4.5; 5,1)	0.139 (b)
_45min	4.1 (3.7; 4,7)	4.8 (4.5; 5.4)	0.321 (b)
_60min	3.8 (3.5; 4,8)	4.7 (4.5; 4.8)	
_75min	3.9 (3.3; 4,8)	4.7 (4.2; 4.9)	
_90min	4.3 (3.3; 4,7)	4.7 (4.3; 5.5)	
_105min	4.5 (4.1; 5,2)	4.6 (4.4; 4.8)	
_120min	3.8 (3.1; 5,0)	4.8 (4.6; 5.4)	
			0.328 (b)
			0.161 (b)
			0.093 (b)
			0.139 (b)
			0.321 (b)
Cumulative dosage_ bolus			
Propofol; mg; (IQR)	185 (150; 200)	175(140; 200)	0.363 (b)
Fentanyl; mg; (IQR)	0.44 (0.40; 0.70)	0.50 (0.4; 0.8)	0.529 (b)
Sufentanil; µg; (IQR)	201.7(115.0; 222.5)	150.3(102.5; 243.3)	0.739 (b)

Piritramid; mg (IQR)	4.5 (4.3; 5.2)	7.5 (6.8; 8.2)	0.121 (b)
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a) Chi²-Test

b) Wilcoxon-Mann-Whitney-Test

Discussion

Our single-center RCT revealed a significant reduction in the incidence of POD by a perioperative administration of dexmedetomidine among elderly patients undergoing either cardiac or noncardiac high-risk surgery ⁽¹⁹⁾. In the present secondary analysis, the perioperative coadministration of dexmedetomidine revealed significantly lower PSi indices, which were not associated with a reduced anesthetic agent or opioid application. Interestingly, despite lower anesthetic depth index values in the dexmedetomidine group, the incidence of POD was also significantly lower, which is a contradiction to previously published RCT trials showing that prolonged deep sedation during general anesthesia is associated with a higher risk of developing POD in elderly patients.⁽⁵⁾

The protective effects of dexmedetomidine in connection with delirium prevention and related outcome parameters have already been demonstrated in previous studies. ^(13, 19, 22) Nevertheless, the exact administration differs considerably between some of the existing studies, as well as the examined patient population. Earlier study results indicate that the patient population, as well as the dosage and timing of dexmedetomidine administration, influences its preventive effects.^(23–25) Age seems to be a relevant risk factor not only for the manifestation of POD but also for the occurrence of deep anesthesia and burst suppression patterns in the EEG.^(2, 26) In our cohort, we focused on an older (≥ 60 years of age) and high-risk surgical population of both noncardiac and cardiac patients undergoing mainly high-risk surgeries (CABG, PPPD, etc.). Accordingly, a high incidence of POD and POCD was expected, as this patient population is known to be most prone to developing cognitive dysfunctions.^(27, 28) For example, the evaluation by Saczynski and colleagues for a cardio-surgical patient group after coronary bypass surgery (CABG) or valve replacement revealed a delirium incidence of 46% ⁽²⁹⁾, which is in accordance with the delirium incidence of our placebo group.

In recent years, the depth of anesthesia and its possible consequences have increasingly become the focus of scientific work. Based on the results of large RCT trials, it is now recommended to monitor the depth of anesthesia with intraoperative frontal EEG neuromonitors in elderly patients to reduce the risk of developing POD by avoiding deep levels of anesthesia. ^(5, 30)

Dexmedetomidine, an alpha-2 adrenoceptor agonist, has sedative, anxiolytic, sympatholytic, analgesic-sparing effects with minimal depression of respiratory function and obtained arousal to stimuli.^(15, 31) Therefore, it is widely used as a sedative or anesthetic adjunct. In addition to a significant reduction in POD in our trial, we would like to emphasize further effects of the perioperative administration of dexmedetomidine, as it seems to have an impact on anesthetic depth and PSi. In the present study

population, over 70% of the patients examined were affected by deep anesthesia during the procedure, with an incidence of 85.2% in the dexmedetomidine group and 58.1% in the placebo group.

In our study, reduced PSi index values occurred despite a significant POD reduction in our dexmedetomidine group without opioid- and anesthetic agent-sparing procedures. This controversial finding may be interpreted in two ways: (1) either the algorithm within the SedLine monitor is not able to reliably indicate the depth of sedation under administration of alpha-2 adrenergic agents or (2) dexmedetomidine itself has a neural effect that prevents POD besides inducing deep sedation. Anesthetic agents inducing unconsciousness act at different molecular targets, including gamma-amino butyric acid type A (GABA_A) agonists, opioid receptor agonists, N-methyl-D-aspartate receptor (NMDA) antagonists and alpha-2 adrenergic agonists. Dexmedetomidine is a highly selective alpha2-adrenergic agonist inducing an increase in delta-band power and coherent spindle oscillations in the frontal brain area during sedation.^(18, 32) This is in contrast to most frequently used anesthetic agents, such as propofol or sevoflurane, which induce besides an increase of delta-band power a highly coherent frontal alpha-band power during unconsciousness.^(33, 34) Since EEG neuromonitor indices depend on inbuilt raw EEG processing algorithms based on fast Fourier transformation and spectral data analysis of shifting EEG epochs, these algorithms have a major impact on the processed index presented during Anesthesia.⁽³⁰⁾ In detail, the PSi is derived from changes in the power spectrum in various EEG frequency bands, frontal hemispheric symmetry and synchronization.⁽²⁰⁾ Since the presented raw EEGs during sedation between GABAergic anesthesia (i.e., propofol, sevoflurane) and alpha-2 adrenergic agonist-induced unconsciousness differ significantly, we assume that the presented PSi during dexmedetomidine application does not reliably indicate the correct level of sedation in these patients. We deduce that patients in the dexmedetomidine group do not undergo deeper sedation levels compared to the placebo group, even though this is indicated by the PSi.

Dexmedetomidine selectively acts on the alpha2-adrenergic receptors of the locus coeruleus projecting to the preoptic area of the hypothalamus, disrupting thalamo-cortical functional connectivity, while maintaining cortico-cortical functional connectivity within the DMN network.⁽¹⁶⁾ During NREM sleep states I and II in humans, the same neuronal functional changes occur: DMN cortico-cortical functional connectivity is preserved, while thalamo-cortical functional connectivity is disrupted.^(35, 36) In many recent studies, the positive effect of sleep on memory consolidation has been shown ^(37, 38), and ICU-related delirium is also triggered by disruption of the circadian rhythm and sleep deprivation.⁽³⁹⁾ Hence, we propose that the application of dexmedetomidine triggers physiological sleep like neuronal oscillations, which improve postoperative cognitive functions in those patients and thereby prevent the development of POD.

In our study, there were no differences in the opiate and hypnotic requirements of the patients between the two groups. To adequately address opioid and hypnotic saving effects through our intervention, the anesthetic levels should have been identical. Since anesthesia was not primarily PSi-guided in our study, i.e., anesthetic depth in both groups was not directly comparable. In contrast, our study results indicate

lower PSi values in the dexmedetomidine group. To be able to take advantage of possible dexmedetomidine-induced hypnotic- and opioid-saving effects, monitoring anesthetic depth, from our point of view, is essential. As our study population gathers different scopes of surgery, opioid requirements, in general, may not be comparable between the two groups or within each group.

Limitations

Intraoperative neurological monitoring was a secondary endpoint in the study and the relatively small sample size in our study is a restriction. One of the main limitations of this analysis is the fact that the PSi was being interpreted without considering the EEG raw data. Additionally, besides the controlled application of the study medication, all other anesthetic agents and opioids were given at clinical requirements by the anesthesiologists in charge. However, since medical applications follow standard operative procedures and we did not see a difference between the two groups, we think this would not have compromised our results.

Conclusion

Perioperative administration of dexmedetomidine prevents POD in elderly patients. EEG neuromonitoring is misleading by indicating very deep states of anesthesia, which are known to be a trigger for POD. These nonreliable EEG-based indices are most likely related to the built-in algorithm not being established to adequately monitor alpha-2 adrenergic-induced unconsciousness. Moreover, since dexmedetomidine establishes NREM sleep-like neuronal activity, this may be the reason for its advantageous effect in older patients to prevent POD, where NREM sleep is known to be beneficial for memory consolidation and executive function.

Declarations

Ethics approval and consent to participate: The study was approved by the Federal Institute for Drugs and Medical Devices (BfArM) and by the Ethics Committee of the Department for Health and Social Affairs (Eudra-CT 2013-000823-15). All patients gave written informed consent obtained by a physician.

Consent for publication: The publication has been approved.

Availability of data and materials: The datasets generated and analyzed during the current study are not publicly available due to German data privacy protection regulations for clinical trials according to the Federal Institute for Drugs and Medical Devices but are available from the corresponding author on reasonable request.

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Figures

CONSORT Flow Diagram Neuropodex

Figure 1

CONSORT Flow Diagram Flowchart of the study design including primary and secondary analysis.

Figure 2

Incidence of PSi Reduction Percentage of mean PSi level below 25 during intraoperative situation according to the dexmedetomidine vs. placebo group.

Figure 3

Depth of Anesthesia/Patient state index The mean patient state index (PSi) was evaluated throughout the entire surgery. The mean PSi values in the dexmedetomidine group (SD) were 28,17 (10,35) and 33,55 (11,31) in the placebo group using mixed-model ANOVA. There were statistically significant main effects for both time ($p=0.000$) and group ($p=0.000$).