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ORIGINAL RESEARCH

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The influence of different application patterns of propofol on the sedation courses during drug-induced sleep endoscopy

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Abstract

Objective: The course of sedation during drug-induced sleep endoscopy (DISE) depends on the application pattern of the sedative drug. The depth of sedation should imitate light and deep sleep as well. Moreover, there should be as many breathing cycles as possible available for observation during light and deep sedation. The aim of the study was to evaluate different rates of propofol application with respect to the achieved depth and length of the course of sedation.

Methods: Sixty-three consecutive patients with obstructive sleep apnea and/or snoring undergoing DISE were randomly sedated by propofol perfusion at seven different application patterns: 14, 16, 18, 19, 20, 22 mg/kg/h (0.233, 0.267, 0.3, 0.317, 0.333, 0.367 mg/kg/min) per perfusor and individual bolus application 10 mg each. Sedation depth was monitored by BiSpectral Index™ (BIS). The influence of baseline parameters and the courses of sedation were analyzed.

Results: The application rate was the only factor that influenced the depth of sedation. Basic parameters (gender, age, body mass index, apnea-hypopnea index) had no influence on the depth of sedation. The sedation depth was dependent on the rate of propofol application. Regimes at 14 and 16 mg/kg/h as well as bolus application did not reach BIS levels below 50 representing deep sleep. Propofol doses of more than 20 mg/kg/h led to rapid decreases of sedation levels below deep sleep niveau. Propofol rates between 18 and 20 mg/kg/h enable BIS levels below 50 representing deep sleep and providing enough breathing cycles for observation.

Conclusion: Lower application rates of propofol provide slower courses of sedation and shallower depths of sedation. A rate of 14 mg/kg/h might be appropriate to reach a sedation plateau at light sleep. A rate of 18 mg/kg/h leads to a sedation, corresponding to deep sleep. The combination of both rates might be a suitable pattern for performing sedation-controlled DISE.

Level of evidence: 2: Randomized trial.

KEYWORDS
BIS, DISE, obstructive sleep apnea, OSAS, sedation depth

1 | INTRODUCTION

Drug-induced sleep endoscopy (DISE) is currently regarded as the most appropriate method to detect the level and patterns of obstruction in patients with sleep-disordered breathing.[1–4] Different sedative drugs (propofol, midazolam, dexmedetomidine) and patterns of application (bolus injection, sedation depth-controlled, target-controlled infusion [TCI]) are commonly performed and the obtained results of DISE vary between the applied drugs and patterns.[3,5–7] Even when using a single drug like propofol, the results of the DISE may vary depending on the dose and flow rate of the applied propofol.

Numerous publications provide evidence that the levels, patterns, and intensity of the collapse of the upper airway can change depending on the depth of sedation.[8–11]

Therefore, it seems appropriate to monitor the depth of sedation during DISE aiming to reach a level of sedation which imitates different sleep stages of natural sleep. BiSpectral Index™ (BIS) is used as a common method for measuring the depth of sedation during DISE. Arbitrary values from 100 (awake) to 0 (deepest sedation) represent the state of sedation. According to several publications, natural sleep stages of N2 (light sleep) and N3 (deep sleep) correspond to BIS values of approximately 70–55 and 50–35.[12–16] On this basis, DISE should be performed up to BIS values between 50 and 35 representing deep sleep.

Despite the knowledge about the effect of different sedative drugs and application patterns there is no general recommendation for the performance of DISE.[3]

Taking these considerations into account, DISE should be conducted under two requirements:

1. Sedation depth should reach levels (BIS values) representing deep sleep.
2. The course of sedation needs to be slow enough to provide an adequate number of breathing cycles, which can be classified by the observer at a certain level of sedation.

The aim of the study was to evaluate the influence of different application rates of propofol and to detect a dose–response correlation between propofol and sedation depth and time.

The following hypotheses were to be tested:

1. The rate of propofol application is the main (only) factor influencing the depth of sedation.
2. The depth of sedation (measured with BIS) depends on the application rate of propofol in terms of a dose–effect relationship.

2 | METHODS

2.1 | Subjects and study design

Patients suffering from documented obstructive sleep apnea (OSA) and/or snoring were consecutively included in the study between November 2019 and August 2021. With the intention of testing five predictors (application rate, gender, age, body mass index [BMI], apnea-hypopnea index [AHI]) as influencing factors for the depth of sedation, a sample size between 5 and 10 per predictor was aimed for ($n \geq 50$).[17,18] The application rate of propofol was randomly assigned. Written informed consent was obtained from all participants. The prospective, interventional, single-center study was approved by the Ethics Board of Landesärztekammer Brandenburg (ethic board ID: AS 108(bB)/2019, PROMISE) and registered at the German Medical Trail Register (DRKS-ID: DRKS00028603).

2.2 | DISE

DISE was performed in an operation room with subdued lighting and quiet environment, without premedication in a supine position monitored by an anesthesiologist. Local anesthesia (1% lidocaine spray) was applied endonasaly. Propofol 1% MCT (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) was used for sedation and was given in the following doses: 14, 16, 18, 19, 20, 22 mg/kg/h (0.233, 0.267, 0.3, 0.317, 0.333, 0.367 mg/kg/min) by infusion pump and manual boli of 10 mg each for a separate group. The depth of sedation was monitored by BIS (BIS VISTA™ Monitoring System, Aspect Medical Systems, Inc., Norwood, MA, USA) using BIS™ Quatro Sensor (Covidien, Neustadt/Donau, Germany).

The BIS scale ranges from 100 to 0 representing a maximum level of alertness at BIS 100 and a maximal sedation at BIS 0. The curve of the depth of sedation was recorded over time manually at time intervals of 10 s.

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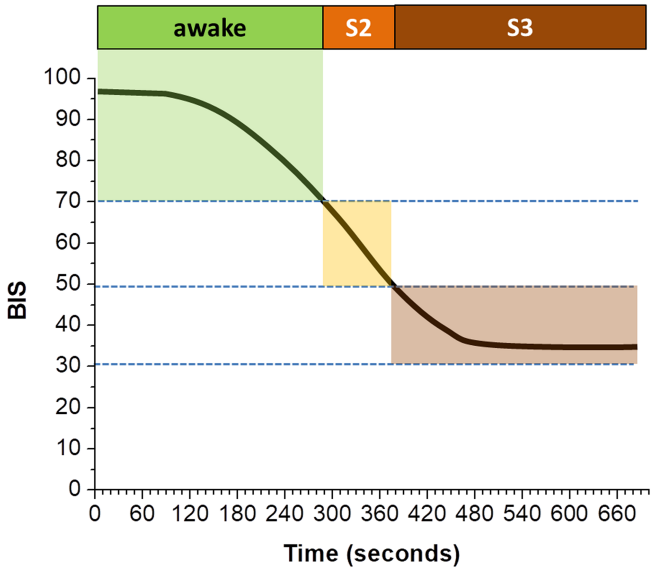

FIGURE 1 Hypothetical sedation curve for DISE. The depth of sedation is plotted on the *y*-axis in BIS values. BIS values between 100 and 70 represent the waking state. Light sleep (S2) corresponds to BIS values between 70 and 50, whereas deep sleep (S3) corresponds to BIS values between 50 and 30. The time curve is shown on the *x*-axis. The sedation curve shows a slow response at the beginning, which can be explained by a flooding phase of the propofol. A plateau phase may occur toward the end of the examination. BIS, BiSpectral Index™; DISE, drug-induced sleep endoscopy.

Flexible endoscopy was performed with a bronchoscope with included suction and an outer diameter of 3.7 mm (11002 BD1, Karl Storz, Tuttlingen, Germany). Any salivation that occurred could be suctioned off if necessary.

If necessary, oxygenation of the breathing air was carried out in the event of excessive hypoxia due to induced obstructions. If necessary, the Esmarch maneuver was temporarily performed to open the upper airways, enable breathing and thus increase blood oxygen saturation.

The prolonged occurrence of central apneas led to exclusion from the study. In these cases, the administration of propofol was stopped and manual mask ventilation was performed. If breathing activity resumed, DISE was continued independently of the study.

2.3 | Sedation parameters

The key values were the BIS values which were reached under the specific application rate of propofol. BIS values between 100 and 70 were considered as awake. Values between 70 and 50 intended to imitate light sleep (sleep stage S2). Deep sleep (slow wave sleep) is imitated at BIS levels between 50 and 30 (sleep stage S3). The time taken to reach a certain depth of sedation is documented for the individual participants. The evaluation is carried out separately for the groups with different sedation rates. A hypothetical sedation curve is given in Figure 1.

A sleep-like sedation state with a sedation depth of at least BIS 70–50 was achieved in all included participants. An assessment of the tendency of the upper airway to collapse for further treatment planning was possible for each participant, even if deeper sedation could not be achieved in some subjects.

2.4 | Statistical analysis

Descriptive data analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). In addition to the application rate of propofol, the factors gender, age, BMI, and AHI should be analyzed as influencing factors on the depth of sedation. The Kolmogorov–Smirnov test was used to determine the normal distribution. A stepwise linear regression model was calculated to evaluate the influence of different variables on the depth of sedation.

3 | RESULTS

3.1 | Patients' baseline data

Sixty-six patients were initially enrolled. Three patients were excluded from the study due to inadequate sedation during DISE. These patients showed a rapid onset of central apnea, which hindered the continuation of the study.

Finally, 63 participants, 47 male and 16 female were included in the study. The mean age of all participants was 49.86 years (SD 13). The mean BMI was 30.22 (SD 4.48). The mean AHI was 27.17 (SD 12.15). The values for the specific application groups of propofol are given in Table 1. The normal distribution was tested using the Kolmogorov–Smirnov test (KS-test). All subgroups were normally distributed in terms of age and BMI as well as for the most groups of the AHI except the dose group 20 mg/kg/h for the AHI.

3.2 | Factors influencing the depth of sedation

Gender, age, BMI, AHI, and rate of propofol application were tested for influence on the depth of sedation defined by the minute of the DISE by stepwise multiple regression. The propofol-bolus group needed to be excluded from the test because the propofol application did not correspond to a numerical order. The application rate was the only factor influencing the depth of sedation whereas gender, age, BMI, and AHI did not affect the sedation depth (*F*-value ≤0.05). The coefficients of determination (R^2) for the respective minutes were (minute/R^2): 1/0.099; 2/0.094; 3/0.185; 4/0.221; 5/0.218; 6/0.177; 7/0.474; 8/0.499; 9/0.500; 9/0.267; 10/0.297. At minutes 7, 8, and 9, the application rate is the main factor influencing the depth of sedation at around 50%. No other influencing factors can be identified on the basis of the available data.

TABLE 1 Baseline data of the participants.

	Propofol (mg/kg/h)							
	14 mg	16 mg	18 mg	19 mg	20 mg	22 mg	Bolus	Total
N	6	11	15	7	10	6	8	63
Gender								
Male	6	8	13	5	5	5	5	47
Female	0	3	2	2	5	1	3	16
Age								
Mean	54.33	44.45	47.80	53.14	47.30	55.50	53.88	49.86
95% CI upper bound	59.87	54.17	56.14	68.95	54.75	66.62	62.94	53.13
95% CI lower bound	48.79	34.74	39.46	37.34	39.85	44.38	44.81	46.58
Median	55.50	41.00	54.00	59.00	50.50	60.50	54.00	54.00
Standard deviation	5.28	14.46	15.05	17.09	10.41	10.60	10.84	13.00
Minimum	47.00	24.00	27.00	25.00	30.00	38.00	37.00	24.00
Maximum	60.00	67.00	72.00	77.00	62.00	64.00	71.00	77.00
p (KS-test)	0.200	0.200	0.137	0.200	0.200	0.109	0.136	0.000
BMI								
Mean	30.75	29.95	29.21	31.28	30.25	27.79	32.94	30.22
95% CI upper bound	34.28	33.66	31.44	34.92	34.11	30.10	36.87	31.35
95% CI lower bound	27.22	26.23	26.99	27.64	26.39	25.47	29.00	29.09
Median	30.27	29.05	28.41	32.05	28.85	27.90	34.39	29.05
Standard deviation	3.37	5.53	4.02	3.93	5.40	2.20	4.71	4.48
Minimum	27.47	21.83	23.70	26.64	25.18	24.22	25.61	21.83
Maximum	34.88	39.64	39.26	36.93	41.05	31.14	38.57	41.05
p (KS-test)	0.124	0.200	0.200	0.200	0.200	0.155	0.200	0.001
AHI								
Mean	30.27	24.56	23.40	29.46	32.59	26.13	27.51	27.17
95% CI upper bound	45.68	34.48	27.90	38.70	44.60	34.19	36.76	30.23
95% CI lower bound	14.85	14.65	18.90	20.21	20.58	18.08	18.26	24.11
Median	28.55	21.50	22.00	29.00	24.95	25.90	28.80	25.00
Standard deviation	14.69	14.76	8.13	10.00	16.79	7.67	11.06	12.15
Minimum	11.40	7.80	11.50	13.00	15.80	13.70	11.40	7.80
Maximum	49.00	50.40	39.40	39.80	69.70	34.70	46.00	69.70
p (KS-test)	0.200	0.070	0.200	0.200	0.032	0.200	0.200	0.003

Note: Baseline data (gender, age, body mass index [BMI], apnea hypopnea index [AHI]) are displayed for the different subgroups of propofol application rates and for the entire cohort.
Abbreviations: CI, confidence interval; *p* (KS-test), test for normal distribution (Kolmogorov–Smirnov-test).

3.3 | Courses of sedation

Lower application rates of propofol lead to longer sedation courses which is demonstrated by higher mean and median BIS values at the 1-min intervals. Toward the end of the sedation curves, there is an increasing overlap of bounds of the confidence intervals, which indicates an approach to a sedation plateau. This plateau effect is also recognizable in the raw data and mean value curves (Figure 2), as well as in the box plots of the specific application rate of propofol (Figure 3A–F, box plots). The BIS values over the time for the different rates of propofol are given in Figure 3A–F as raw data curves every 10 s (left side) and box plots at 1-min intervals (right side). The numerical values are displayed in Table 2.

3.4 | Bolus application of propofol

In addition to the participant groups with sedation defined by the perfusion rate, the bolus application of propofol was investigated as well. According to the data of Table 2 and Figure 4 we were able to achieve a sedation level between BIS 50 and 70 (S2 sleep) but could not obtain BIS levels below 50 for S3 sleep.

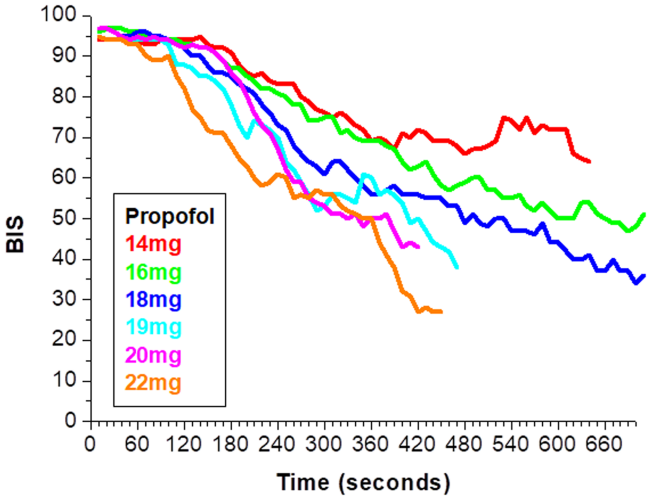

FIGURE 2 Mean values of each application rate of propofol. There is a dose–response shift to the left with higher application rates of propofol (mg/kg/h). In addition, there is a shift in the sedation curves toward lower BIS values with higher application rates of propofol. An implied plateau formation can be recognized at application rates of 14, 16, and 18 mg/kg/h. The raw sedation curves of each application rate is given in Figure 3. BIS, BiSpectral Index™.

4 | DISCUSSION

The present study investigated the influence of different application patterns of propofol on the sedation courses during DISE measured by BIS.

The initial hypotheses were confirmed as follows.

1. The rate of propofol application is the main factor influencing the depth of sedation.
2. A dose–effect relationship between the depth of sedation (BIS) and the application rate of propofol is present.

- Lower application rates lead to a slower course of sedation and a shallower sedation depth.
- Higher application rates lead to a faster onset of sedation and deeper sedation.

The higher the application rates of propofol, the faster the onsets of sedation. From a clinical point of view, this means that with a higher application rate, less time is available for analyzing the breathing cycles at a certain sedation depth.

4.1 | Clinical significance of sedation speed

According to the current knowledge, natural sleep corresponds to the following BIS values: wake: 100–70, S2: 70–50, S3: 50–30, REM: 70–30.[12–14,19] Given the assumption that patients fall into a sleep-like state below a BIS value of 70, only the examination periods after reaching BIS 70 and lower can be used for evaluation. As a concrete example with mean BIS values taken from Table 2, participants in the 22 mg propofol group reach BIS 70 after approximately 3 min and BIS 50 after 6 min, which creates an observation window of 3 min for imitated S2 sleep. Participants in the 16 mg propofol group reach BIS 70 in minute 6 and BIS 50 in minute 10, which provides an observation window of 5 min at S2.

It needs to be considered that an adult individual shows approximately 15 breathing cycles per minute when sleeping. Referring to the concrete example participants of the 20 mg group reveal 45 breathing cycles and individuals of the 16 mg group 75 breathing cycles for observation at S2.

From the clinical point of view, it needs to be considered that approximately one third of the breathing cycles cannot be observed adequately due to limited visibility (e.g., salive on the tip of the endoscope or contact to pharyngeal structures). In the example mentioned above approximately 30 breathing cycles might remain for the 20 mg propofol group in contrast to 50 breathing cycles for the 16 mg group. Additionally, the endoscope needs to be repositioned several times during DISE to observe the cranial oropharyngeal level (velum) and the caudal oropharyngeal level (tongue base) during the course of sedation. This repositioning causes another loss of observable breathing cycles with the result that another 5–6 cycles get lost. In total, approximately 12 cycles remain for observation for each anatomical level (cranial vs. caudal oropharynx) during light at 20 mg propofol and 22 cycles at 16 mg propofol during the whole DISE procedure.

On this background it is essential to get a sedation curve as slow as possible to obtain as many observable breathing cycles as possible at a certain sedation level.

4.2 | Clinical significance of the depth of sedation

Additionally, recent publications report changes of the levels of obstructions and variable collapse patterns depending on the depth of sedation.[9,10,20,21] On this basis, it can be concluded that sleep stages S2 and S3 should be reached during DISE to get comprehensive results. In terms of BIS, values of below 70 and below 50 need to be achieved to imitate light and deep sleep, respectively.

The data presented show that low application rates do not enable deep sedation states. According to the data in Table 2 and the graphs in Figure 3A it can be stated that participants of the 14 mg propofol group remain at BIS levels around 70 and participants of the 16 mg cohort do not fall below BIS 50. These data provide evidence that low doses of propofol (≤16 mg/kg/h) do not induce BIS values representing S3 stages. On the other hand participants of the 22 mg propofol group do fall below BIS 30 tending to be more sedated than necessary for DISE with the risk of developing central apneas.

4.3 | Interpretation of the sedation plateaus

An additional observation of the study was the setting of sedation plateaus at certain BIS levels corresponding to the selected application

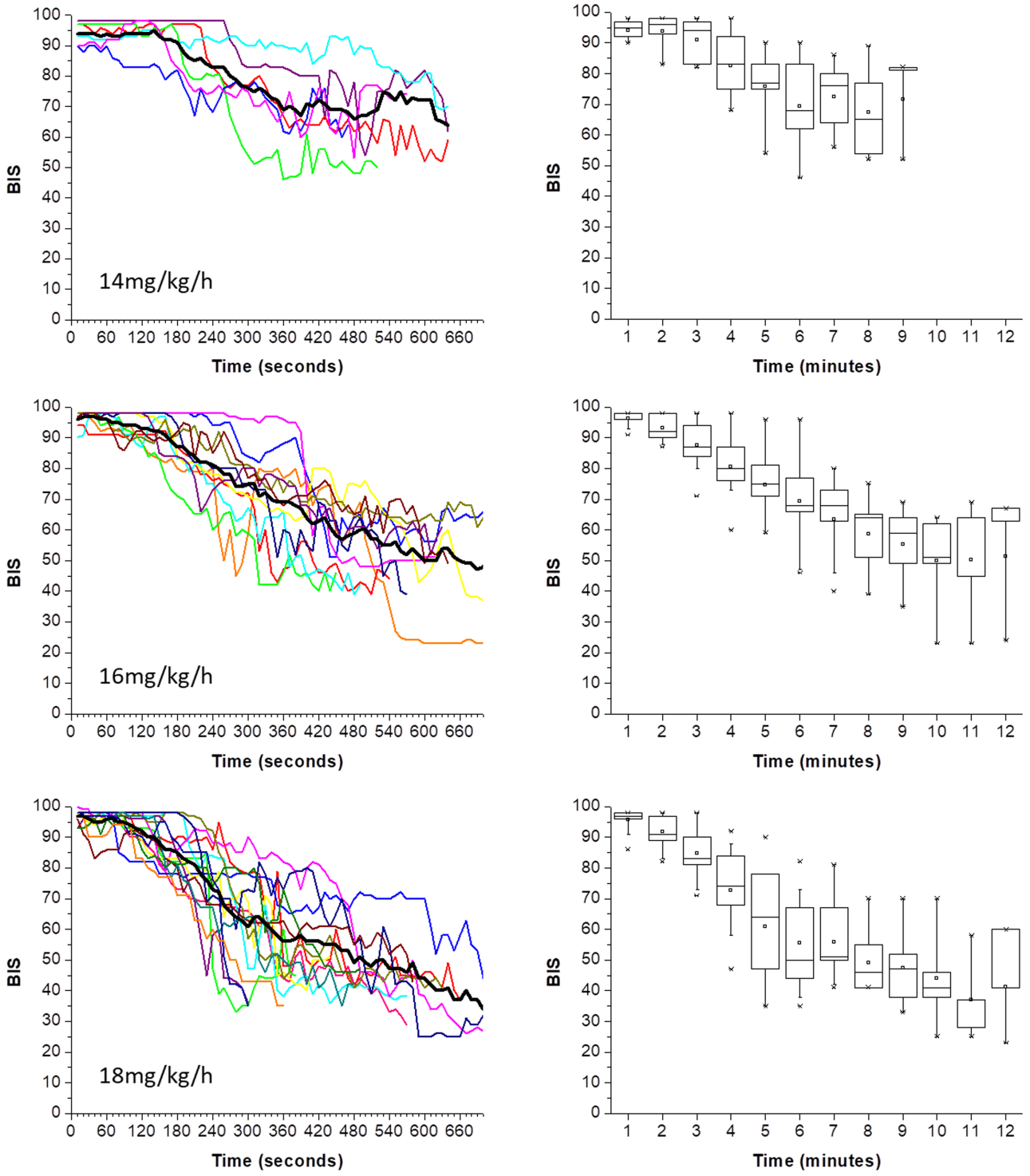

FIGURE 3 (A–F) Course of sedation under different application rates of propofol. In the left panel the sedation courses of each patient are given as an individual colored line. The mean curves for each dosage is displayed as a black line (A, 14 mg/kg/h; B, 16 mg/kg/h; C, 18 mg/kg/h; D, 19 mg/kg/h; E, 20 mg/kg/h; F, 22 mg/kg/h). The depth of sedation was measured every 10 s. The panels on the right show the box plots at 1-min intervals during the course of the investigation (box plots: median and 25%/75% percentile, square = mean; whiskers 5%/95%; outliers as single display).

rate. When looking at the boxplots (Figure 3A–C), the propofol groups from 14 to 18 mg/kg/h show the development of a plateau toward the end of the sedation curve. Apparently, saturation of the propofol effect is achieved at the selected application rates.

4.4 | Comparison with other sedation regimes

At the propofol doses of 14 mg/kg/h, 16 mg/kg/h and the manual boli of 10 mg, a deep sleep-like sedation (S3 sleep stage) was not

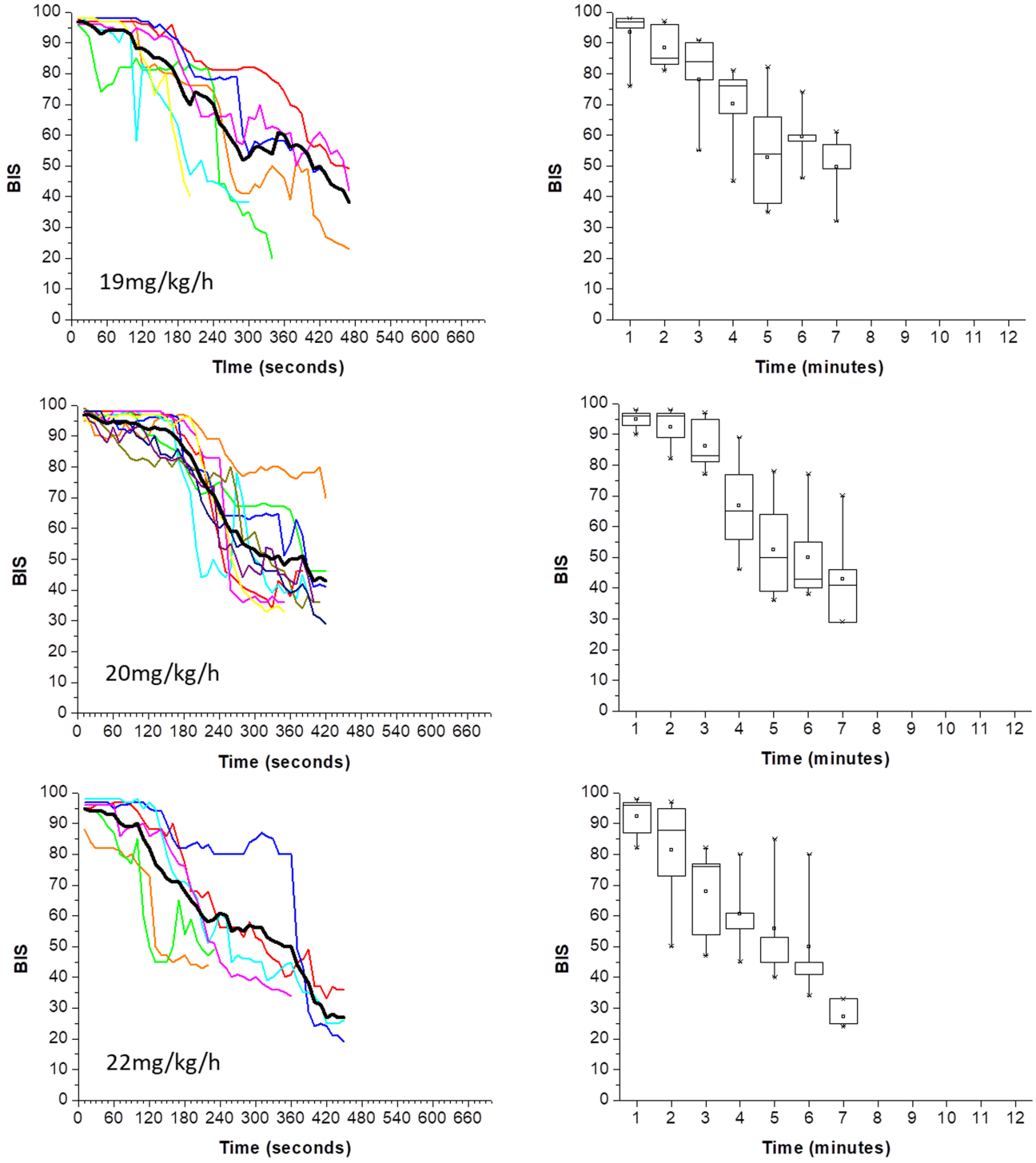

FIGURE 3 (Continued)

achieved. After a short build-up phase, the BIS value fell and leveled off at around 60–70. Here the decomposition of propofol seems to be faster than the flooding or even create a steady state. Therefore, these dosages do not fit the requirements for a deep sleep observation.

This is in line with the concept of TCI, which was first time evaluated by Kruger-Thiemer in 1966.[22] Since that time a lot of efforts have been made to improve the concept, especially for propofol. Currently the algorithms of Schnider and Marsh are used worldwide and are integrated in different syringe-pumps.[23,24]

In an interesting study of Coppens et al. BIS was used to evaluate sedation depth, when comparing Schnider and Marsh concepts after induction with a infusion rate of 3000 mg/h propofol until loss of response to name calling.[25] They demonstrated that using different

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TABLE 2 BIS values during sedation.

Time (s)	60	120	180	240	300	360	420	480	540	600	660	720	780
Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Propofol 14 mg													
N	6	6	6	6	6	6	6	5	4	3	2	2	2
Mean	94.00	93.83	90.83	82.67	75.83	69.33	72.33	65.60	74.25	71.67	68.50	56.50	54.50
95% CI upper bound	97.32	99.75	98.09	94.19	88.52	85.72	83.78	86.13	86.11	113.99	100.27	215.33	−66.21
95% CI lower bound	90.68	87.92	83.58	71.14	63.15	52.95	60.88	45.07	62.39	29.34	36.73	102.33	175.21
Median	93.50	95.50	92.50	81.50	76.50	67.50	74.00	62.00	74.50	81.00	68.50	56.50	54.50
Standard deviation	3.16	5.64	6.91	10.98	12.09	15.62	10.91	16.53	7.46	17.04	3.54	17.68	13.44
p (KS-test)	0.200	0.177	0.200	0.200	0.083	0.200	0.200	0.200	–	–	–	–	–
Propofol 16 mg													
N	11	11	11	11	11	11	11	10	9	7	4	3	2
Mean	96.27	93.18	87.45	80.55	74.64	69.27	63.36	58.70	55.33	50.00	50.25	51.33	61.00
95% CI upper bound	97.89	96.30	92.95	87.54	81.95	79.51	72.14	66.91	64.08	62.70	83.51	110.35	86.41
95% CI lower bound	94.65	90.06	81.96	73.55	67.32	59.03	54.58	50.49	46.59	37.30	16.99	−7.68	35.59
Median	98.00	92.00	87.00	80.00	75.00	68.00	68.00	62.50	59.00	51.00	54.50	63.00	61.00
Standard deviation	2.41	4.64	8.18	10.42	10.89	15.25	13.07	11.47	11.38	13.74	20.90	23.76	2.83
p (KS-test)	0.004	0.055	0.200	0.200	0.200	0.200	0.062	0.026	0.200	0.200	–	–	–
Propofol 18 mg													
N	15	15	15	15	15	13	11	10	8	5	4	3	1
Mean	95.87	91.80	84.73	72.80	60.80	55.62	55.82	49.10	47.38	44.00	37.00	41.33	–
95% CI upper bound	97.65	94.78	89.42	79.54	70.69	64.66	64.30	56.23	57.25	64.46	60.71	87.30	–
95% CI lower bound	94.08	88.82	80.05	66.06	50.91	46.57	47.34	41.97	37.50	23.54	13.29	−4.63	–
Median	97.00	91.00	83.00	74.00	64.00	50.00	51.00	44.00	46.50	41.00	32.50	41.00	–
Standard deviation	3.23	5.37	8.46	12.17	17.86	14.98	12.62	9.96	11.81	16.48	14.90	18.50	–
p (KS-test)	0.000	0.190	0.200	0.200	0.200	0.200	0.044	0.050	0.200	0.200	–	–	–
Propofol 19 mg													
N	7	7	7	6	6	4	4	2	2	1	1	1	0
Mean	93.57	88.29	78.00	70.17	52.67	59.50	49.75	36.00	38.50	–	–	–	–
95% CI upper bound	100.87	94.82	90.82	84.02	72.04	77.76	70.18	201.18	235.45	–	–	–	–
95% CI lower bound	86.27	81.75	65.18	56.32	33.30	41.24	29.32	−129.18	−158.45	–	–	–	–
Median	97.00	85.00	84.00	75.00	47.50	59.00	53.00	36.00	38.50	–	–	–	–
Standard deviation	7.89	7.06	13.86	13.20	18.46	11.47	12.84	18.38	21.92	–	–	–	–
p (KS-test)	0.003	0.200	0.200	0.150	0.200	–	–	–	–	–	–	–	–

TABLE 2 (Continued)

Time (s)	60	120	180	240	300	360	420	480	540	600	660	720	780
Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Propofol 20 mg													
N	10	10	10	10	10	8	5	*2*	*0*	*0*	*0*	*0*	*0*
Mean	95.00	92.30	86.30	66.90	52.60	50.00	43.00	34.00	–	–	–	–	–
95% CI upper bound	97.16	96.20	91.62	76.72	62.60	62.19	63.91	122.94	–	–	–	–	–
95% CI lower bound	92.84	88.40	80.98	57.08	42.60	37.81	22.09	−54.94	–	–	–	–	–
Median	96.00	93.00	82.50	64.50	49.50	42.50	41.00	34.00	–	–	–	–	–
Standard deviation	3.02	5.46	7.44	13.73	13.99	14.58	16.84	9.90	–	–	–	–	–
p (KS-test)	0.144	0.074	0.036	0.200	0.200	0.023	0.200	–	–	–	–	–	–
Propofol 22 mg													
N	6	6	6	4	4	4	3	*2*	*1*	*0*	*0*	*0*	*0*
Mean	92.50	81.50	67.83	60.50	55.75	50.00	27.33	23.00	–	–	–	–	–
95% CI upper bound	99.29	99.97	82.58	83.76	87.93	82.64	39.59	99.24	–	–	–	–	–
95% CI lower bound	85.71	63.03	53.09	37.24	23.57	17.36	15.08	−53.24	–	–	–	–	–
Median	95.50	87.00	73.50	58.50	49.00	43.00	25.00	23.00	–	–	–	–	–
Standard deviation	6.47	17.60	14.05	14.62	20.22	20.51	4.93	8.49	–	–	–	–	–
p (KS-test)	0.060	0.200	0.200	–	–	–	–	–	–	–	–	–	–
Propofol bolus													
N	8	8	8	8	8	8	7	7	7	5	3	*2*	*2*
Mean	92.38	79.75	67.38	64.63	65.25	58.13	59.71	56.86	54.00	54.20	60.67	57.50	63.50
95% CI upper bound	97.51	89.25	78.69	73.30	75.06	68.74	68.82	67.08	63.23	67.35	101.51	229.03	107.97
95% CI lower bound	87.24	70.25	56.06	55.95	55.44	47.51	50.61	46.64	44.77	41.05	19.82	114.03	19.03
Median	95.00	81.00	74.50	66.50	70.50	54.00	60.00	58.00	52.00	48.00	67.00	57.50	63.50
Standard deviation	6.14	11.36	13.53	10.38	11.73	12.70	9.84	11.05	9.98	10.59	16.44	19.09	4.95
p (KS-test)	0.046	0.200	0.053	0.200	0.149	0.200	0.200	0.200	0.069	0.102	–	–	–
Total													
N	63	63	63	60	60	54	47	38	31	21	14	11	7

Note: BIS values for the specific application rates (propofol, mg/kg/h) are given at 1-min intervals. The normal distribution (KS-test) was calculated up to a number of five participants (*N*). The mean values were calculated up to a number of four participants. Time points with two or fewer participants are not included in the curve calculation (*N* in italics). The mean values of each application rate are displayed as a sedation curve in Figure 2.

Abbreviation: BIS, BiSpectral Index™.

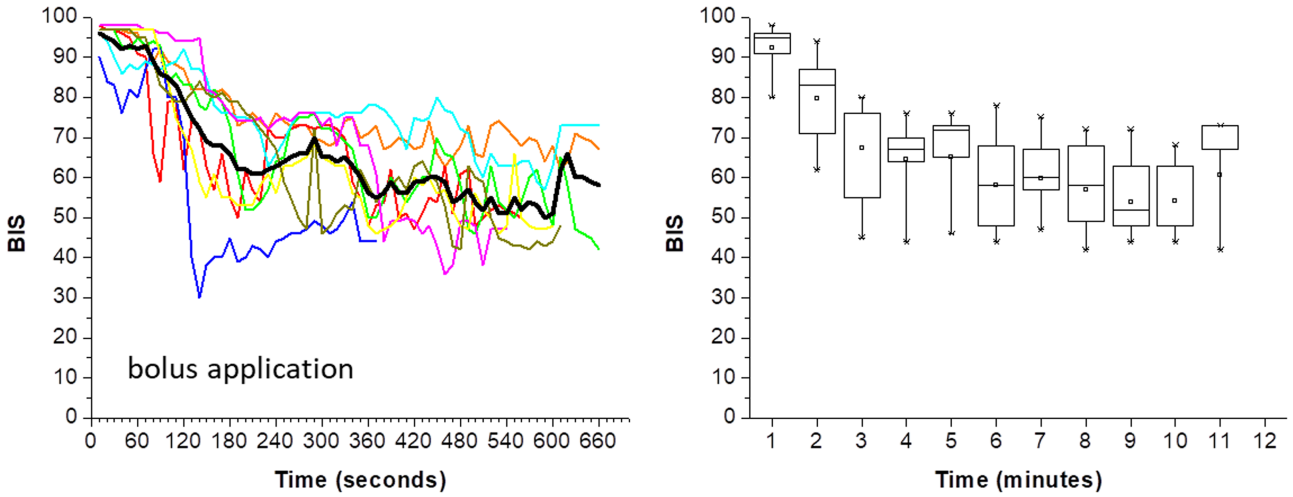

FIGURE 4 Course of sedation under bolus application of propofol. In the left panel the sedation courses of each patient are given as an individual colored line and the mean curve is displayed as a black line. Box plots at 1-min intervals are given on the right analog to Figure 3. In most cases, sedation corresponding to S3 stages could not be achieved. A sedation plateau occurs at BIS values that correspond to S2 stage. BIS, BiSpectral Index™.

concepts is leading to different, more or less constant, BIS levels after 20 min, which is in line with our investigation. Also in DISE patients TCI was evaluated by de Vito et al, but in contrast to our study without focusing sedation depth.[26]

de Vito et al. recommend 50–100 mL/h for manually controlled infusion depending on the patient response, which is a lower dosage compared to our study and based on our data this dose does not provide a sufficient depth of sedation.[3] This working group recommends the use of a syringe infusion pump with TCI technology as the standard mode for sedation if propofol is the drug chosen for sedation, or a syringe infusion pump, if a TCI method is not available.

Padiyara et al. explored sedation via propofol infusion at 50–150 µg/kg/min (3–9 mg/kg/h) titrated according to the BIS values to obtain the required sedation depth,[5] which is also a lower dosage compared to our study. In our investigations this dosage would not have guaranteed a sufficient depth of sedation.

Capasso et al. compared VOTE classification findings with propofol versus dexmedetomidine.[27] The dosage of propofol used was 6 mg/kg/h (converted) with intermittent boli at 0.1–0.3 mg/kg as required for maintenance. However, no apparative measurement of the depth of sedation was carried out.

4.5 | Clinical significance for DISE

One of the main conclusions of the study is that low application rates of propofol do not allow for sufficiently deep sedation, but do allow for a long observation period. In contrast, high application rates result in rapid and excessively deep sedation. Furthermore, a plateau formation of the BIS curves was observed at low application rates.

This emphasizes the importance of a sedation depth measurement during the DISE which is in line with other publications which propagated the BIS as an adequate tool to measure the depth of sedation during DISE to identify sedation levels which imitate natural sleep stages.[16,28,29]

4.6 | Limitation of the study

A week point is the limited number of participants. Especially when reaching a BIS plateau more data might provide a more accurate description of the plateau level which might be of clinical relevance.

It is known that REM sleep is also associated with upper airway obstructions and the imitation of REM sleep might be useful during DISE. The use of BIS for distinguishing between different sleep stages is only possible for non-REM sleep (light sleep, N2; deep sleep, N3). BIS values for REM sleep show a wide range between 70 and 30 and cannot be differentiated from N2 and N3 sleep.[12–14,19]

The BIS is a calculated parameter of an exclusively frontal EEG recording based on an unknown algorithm. The imputed response time of about 30 s and the exclusive restriction to the frontal cortex account for a temporal discrepancy to the actual EEG and perhaps the possible inter-subject variability. However, the authors do not see any relevant influence of this technical method limitation on the evaluation of the study results here. Moreover, this temporal delay of the BIS emphasizes the need of a stable plateau of sedation for a period of time of several minutes.

4.7 | Proposal of a BIS-monitored DISE regime

As a consequence of the results of the presented study a DISE regime with appropriate dosages of propofol might be proposed. The application rates of propofol should be high enough to induce sedation levels

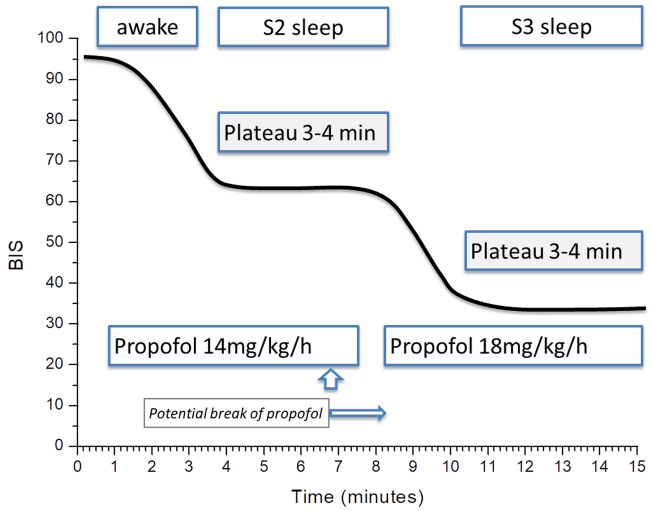

FIGURE 5 Proposal for conducting a DISE. Sedation depth is monitored by BIS. Propofol is administered by infusion pump at a rate of 14 mg/kg/h until a stable plateau corresponding to S2 sleep is reached. The plateau should be maintained to enable the observation of sufficient breathing cycles. A break of propofol administration might be necessary if the BIS values drop too fast. Propofol is increased to 18 mg/kg/h to reach a sedation level corresponding to S3 sleep afterwards. BIS, BiSpectral Index™; DISE, drug-induced sleep endoscopy.

of BIS values imitating S3 sleep on the one hand and low enough to provide a slow course or even a plateau of sedation on the other hand offering as many breathing cycles as possible at light sleep and deep sleep levels.

Similar to our study Lo et al.[30] performed DISE by intermittent bolus propofol application to reach different states of sedation (light: BIS 65–75; deep: 50–60) corresponding to S2 and S3 sleep, respectively. Based on their data and our own, we have developed a proposal for a DISE regime (Figure 5). The aim is to achieve long-lasting sedation plateaus in light sedation (S2 sleep) and deep sedation (S3 sleep) to have enough breathing cycles available for observation. The examination starts with 14 mg/kg/h propofol administered by infusion pump until a sedation level of approximately BIS 70 is reached. If the sedation is too strong and the BIS value drops too quickly without leveling off at a plateau, a pause in the application of propofol can be taken. After a sufficient plateau phase at S2 sleep level, the application rate of propofol is increased to 18 mg/kg/h and a sedation level corresponding to S3 sleep is aimed for.

5 | CONCLUSION

When choosing a propofol regime for DISE it should be considered to have enough time to examine the upper airway during sedation levels representing light and deep sleep as well. The lower the rate of propofol the slower the course of sedation and shallower the depth of sedation. Based on the presented data, 14 mg/kg/h appears to be an appropriate application rate to reach a sedation depth corresponding to S2 sleep including a sedation plateau at S2. A sedation rate of 18 mg/kg/h leads to a deeper sedation, which corresponds to the S3 stage. A combination of both rates might help to perform a sedation-controlled DISE providing long observation windows at S2 and S3 stages.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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