

Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients

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Abstract

Context: Sleep deprivation is a common problem on intensive care units (ICUs) influencing not only cognition, but also cellular functions. An appropriate sleep-wake cycle should therefore be maintained to improve patients' outcome. Multiple disruptive factors on ICUs necessitate the administration of sedating and sleep-promoting drugs for patients who are not analgo-sedated. **Aims:** The objective of the present study was to evaluate sleep quantity and sleep quality in ICU patients receiving either propofol or flunitrazepam. **Settings and Design:** Monocentric, randomized, double-blinded trial. **Materials and Methods:** A total of 66 ICU patients were enrolled in the study (flunitrazepam $n = 32$, propofol $n = 34$). Propofol was injected continuously (2 mg/kg/h), flunitrazepam as a bolus dose (0.015 mg/kg). Differences between groups were evaluated using a standardized sleep diary and the bispectral index (BIS). **Statistical Analysis Used:** Group comparisons were performed by Mann-Whitney U-Test. $P < 0.05$ was considered to be statistically significant. **Results:** Sleep quality and the frequency of awakenings were significantly better in the propofol group (Pg). In the same group lower BIS values were recorded (median BIS propofol 74.05, flunitrazepam 78.7 [$P = 0.016$]). BIS values had to be classified predominantly to slow-wave sleep under propofol and light sleep after administration of flunitrazepam. Sleep quality improved in the Pg with decreasing frequency of awakenings and in the flunitrazepam group with increasing sleep duration. **Conclusions:** Continuous low-dose injection of propofol for promoting and maintaining night sleep in ICU patients who are not analgo-sedated was superior to flunitrazepam regarding sleep quality and sleep structure.

Keywords: Bispectral index, intensive care unit, propofol, sleep

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Introduction

Deficient quality, duration and structure of sleep may have a detrimental effect on the recovery of intensive care patients.^[1-5] Maintaining an adequate sleep-wake cycle with a sufficient night sleep is therefore crucial for these patients. Due to various disrupting factors

on intensive care units (ICU), the administration of sedatives is necessary in most cases to promote night sleep. The most widely used drugs are benzodiazepines like the long-acting flunitrazepam. In general, they tend to prolong sleep duration without improving sleep quality.^[6]

For anesthetics, many studies have documented a sleep-like state by activation or inhibition of different brain regions.^[7-10] Anesthesia in general and propofol in particular seem to reverse the effects of sleep deprivation^[11,12] and show sleep-like electroencephalographic patterns.^[13-15] However evidence of improved sleep quality for ICU-patients is still lacking.^[16]

The objective of this study was to determine the quality and quantity of night sleep in spontaneously

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breathing ICU patients under two different sedation regimes with propofol and flunitrazepam. Sleep duration and sleep quality were evaluated using a modified "Pittsburgh sleep diary (PghSD)"^[17] and by simplified electroencephalogram (EEG) monitoring with the bispectral index (BIS).

Materials and Methods

Study design

The prospective randomized double-blinded study was approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each participant. Only patients without pre-existing sedation, mechanical ventilation, hepatic diseases, renal insufficiency or cerebral diseases who were admitted after surgical intervention to anesthesiological ICU were eligible for this study. As environmental noise is a considerable factor influencing patients' sleep in ICU medical interventions and sounds were reduced to a minimum according to clinic standards and documented by the nursing staff.

After randomization patients were prepared by fixing the BIS electrodes to the skin, connecting the BIS monitor to a laptop and monitoring vital signs such as oxygen saturation, blood pressure and heart rate. Heart rate (bpm) and capillary oxygen saturation (%) were recorded continuously. Depending on the availability of equipment, blood pressure was measured either invasively and continuously or non-invasively and intermittently (every 15 min). Data were collected over a period of 7 h from 11 pm to 6 am.

For comparability, we chose the intravenous route for flunitrazepam since propofol can only be administered parenterally. The drugs were injected after a period of 2 min at rest. Propofol (20 mg/ml) was administered continuously with 2 mg/kg/h over a period of 7 h time. Flunitrazepam was given as a bolus dose over 2 min with 0.015 mg/kg. Drug administration was started at 11 pm propofol infusion was stopped at 6 am. To ensure blinding drugs were given by nursing staff after randomization. Patients were unaware of the used agents.

The day after the study night patients were asked to evaluate their sleep by filling in the sleep diary.^[17]

BIS

The BIS was recorded using the EEG system Aspect A-2000 System XP (Aspect Medical Systems, Natick,

MA, USA). The high and low filters were set to 70 Hz and 0.25 Hz. The notch filter was set to 50 Hz. Four electrodes (BIS-Sensor XP Quatro, Aspect Medical Systems, Natick, MA, USA) were placed on the forehead according to the recommendations of Aspect Medical Systems, three of them on the frontal scalp (electrode one center position 1 cm above the nose, electrode four above the eyebrow) and one on the temporal scalp (electrode three between the eye and hairline). The electrodes were connected through the wire and digital signal converter to the monitor.

Depending on the signal quality index (SQI), the degree of influences of artefacts ("proportion of satisfying measurements"), the suppression ratio, the electromyogram, the BIS and the SQI were displayed on the monitor. All parameters were recorded as 5 s average-values.

Sleep diary

Patients were asked to assess their sleep quality using a standardized sleep diary [amended version of the PghSD].^[17] This was carried out in the afternoon of the first "post-interventional" day, when the patients were fully conscious. Patients were asked to give information on the point of time of falling asleep, the duration of sleep, the number and duration of awakenings and the length of time spent awake. Furthermore, sleep quality, quality of falling asleep, regeneration and refreshment after sleep had to be assessed. The evaluation was done by using school grade-like numbers between one and five. Number one was consistent with "very good" quality and five with "very bad" quality.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics 11.5 for Windows. Group comparisons were performed by Mann-Whitney U-Test. A $P < 0.05$ was considered as statistically significant. Values for epidemiological data were represented as mean \pm SD and for non-parametric data as median (interquartile range). To compare BIS values the overall median of every patient was computed and comparisons between the groups were performed. Five second-values were displayed time dependently for every patient and in summary for both groups. The study period was divided into 1-h sections and corresponding BIS values were compared between groups. According to the results of Sleight *et al.*^[18] BIS values were allocated to sleep stages. By using the BIS monitor alone it was not possible to identify rapid eye movement (REM) sleep. Given that BIS values of light sleep and REM sleep are in the same range they had to be outlined. To minimize artificial variability of the

BIS the data were concentrated to the 2-min median. BIS values ≤ 74 corresponded to slow wave sleep (called sleep stage A), BIS values of 75-89 to light sleep and REM sleep (called sleep stage B) and BIS values ≥ 90 to the awake state (called sleep stage C). Due to the missing data of the row EEG further fragmentation to the different non-REM (NREM) stages was not possible. Correlation analysis was performed with the Spearman Rho correlation. A coefficient $r > 0.4$ and $P \leq 0.05$ was considered to be statistically significant.

Results

Patient characteristics

A total of 66 patients aged between 19 and 83 years ($\bar{X} 60.06 \pm 12.02$) were enrolled for the study. Between groups, no statistical difference was found in gender, age and body weight and body length and body mass index. After excluding one patient with award length of stay of 32 days (propofol group [Pg]) the mean ward length of stay prior to inclusion was (d hh: mm) 0 20:25 ($\pm 0 18:45$) [Table 1]. The majority of patients (92.42%) were treated as urological intermediate care patients. All others were admitted to the ICU due to thoracic or abdominal diseases (mediastinitis, abscess, chronic pancreatitis, abdominal tumor, cholecystitis, insufficiency of an aortic prosthesis). Due to surgical interventions requiring general anesthesia 59 patients (89.4%) in both groups were pre-treated with benzodiazepines and propofol and four patients (Pg $n = 3$, flunitrazepam group [Fg] $n = 1$) with benzodiazepines alone within 48 h prior study inclusion. No patient received antidepressants or neuroleptics.

Vital signs and environmental noise

In general, blood pressure, heart rate and oxygen saturation did not change significantly after administration of the drugs. Three patients sustained a respiratory depression after bolus injection of flunitrazepam. This was handled by insertion of a wendle tube. After these incidents, the complete dose

of flunitrazepam was injected over a period of 2 min. Thereafter no further crucial respiratory alterations occurred. Patients' interventions and environmental noise were comparable between groups.

Sleep diary

The frequency of awakenings was lower in the Pg (median null events) compared with the Fg (median 3.0 events [$P < 0.001$]). Patients who had received propofol reported a maximum of six awakenings. After administration of flunitrazepam patients declared up to thirty awakenings. Median duration of awakenings for Fg was 15:00 min ($P < 0.001$) compared with 00:00 min for Pg. The maximum duration of awakening for Pg was 45:00 min and for Fg 390:00 min. Total sleep duration was similar for both groups (Pg 06:00:00 h, Fg 05:00:00 h [$P = 0.623$]). Sleep quality for Pg was assessed as significantly better (Pg median 2.0, Fg median 3.0 [$P < 0.001$]) [Figure 1]. Results for regeneration and refreshment after sleep were similar to sleep quality and are therefore not displayed. Quality of falling asleep did not differ between groups (Pg median 2.0, Fg median 2.0 [$P = 0.341$]).

BIS

Median bis

BIS data from 56 patients was evaluated. Signal recordings for ten patients (three Pg patients, seven Fg patients) were incomplete and could not be used for analysis. Due to a high number of artefacts in the last 2 h of data registration only the first 5 h were used for analysis as this time period reflects the major sleep episode. Artefacts were mainly caused by sensor dislocation in the line of patients' movement. The overall median BIS value was 76.5. Significantly lower BIS values were recorded in the Pg. The median BIS was 74.05 for Pg compared with 78.7 for Fg ($P = 0.016$) [Figure 2].

BIS in time response

The initial BIS values (Pg median 96.93, Fg median 97.23 [$P = 0.129$]) and the minimum BIS values (Pg median 50.22, Fg 56.09 [$P = 0.08$]) did not differ between groups.

Due to the different pharmacokinetics and the mode of application of the hypnotics used unequal BIS changes over time had to be expected, especially at the beginning of the study period. For the 1st h median, BIS values were significantly lower after injection of flunitrazepam. For the remaining time, lower BIS values were registered for propofol [Table 2, Figure 3].

Table 1: Demographic data for all patients

	Total	Flunitrazepam	Propofol
Gender (♀: ♂)	8; 58	4; 28	4; 30
Age (years)	60.06 \pm 12.02	59.90 \pm 11.02	60.20 \pm 13.00
Body weight (kg)	82.30 \pm 10.86	79.57 \pm 10.46	84.71 \pm 10.78
Body length (cm)	175.55 \pm 7.89	175.13 \pm 7.07	175.91 \pm 8.64
Body mass index (kg \times m ⁻²)	26.72 \pm 3.24	25.94 \pm 3.18	27.42 \pm 3.18
Ward length of stay ^b (t hh: mm)	0 20:25 \pm 0 18:45 ^a	0 23:42 \pm 0 19:14	0 17:53 \pm 0 18:35 ^a

No statistical differences existed between groups. Specifications were done in mean \pm SD. Distribution of gender was declared as absolute frequency. ^aExclusion of an extremal value of 32 days in the Pg; ^bWard length of stay prior the beginning of the study period. SD: Standard deviation; Pg: Propofol group

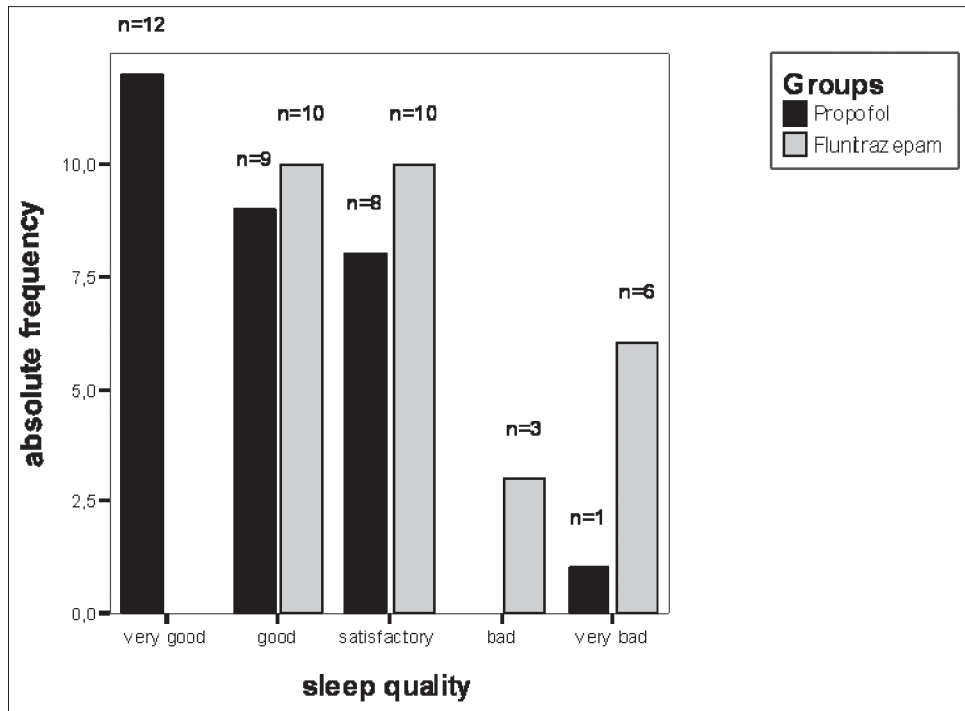


Figure 1: Assessment of sleep quality. 12 patients who received propofol assessed their sleep quality as very good. In contrast, no patient in the flunitrazepam group assessed their sleep quality as very good

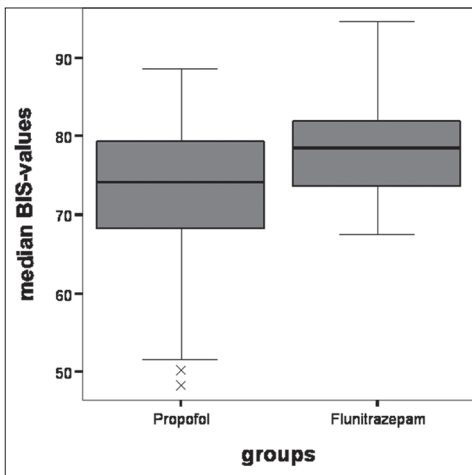


Figure 2: Box plots showing the contribution of median bispectral index values separated for both groups. Crosses demonstrate outliers

Sleep stages

Individual fluctuations of BIS values could be an expression of a progression of sleep stages [Figure 3]. Sleight *et al.*^[18] were able to allocate BIS values to sleep stages. After administration of propofol patients spend a significantly longer time period in deep sleep. After injection of flunitrazepam sleep was characterized mainly by light sleep/REM sleep. Total sleep time, the sum of sleep stages A and B, did not differ between groups. Patients in both groups spent the same time duration in sleep stage C (awake) [Table 3]. This suggests that propofol might be superior to flunitrazepam for promoting deep sleep.

Table 2: BIS medians of the 1st five h

Hour	BIS median		Level of significance
	Propofol	Flunitrazepam	
First	79.38	72.05	P=0.01
Second	65.68	78.90	P=0.002
Third	74.40	79.95	P=0.002
Fourth	73.60	80.30	P=0.007
Fifth	72.95	81.00	P=0.007

After injection of flunitrazepam BIS values rapidly decreased to a minimum. Subsequently values rose over the study period. After the 1st h BIS values were significantly lower for Pg. BIS: Bispectral index; Pg: Propofol group

Arousals and awakenings

Apart from the appearance of different sleep stages the frequency of arousals and awakenings mainly characterizes naturally occurring sleep. Only awakenings of longer than 3 min can be remembered.^[19] Here awakenings longer than 3 min (called awakenings) were distinct from awakenings shorter than 3 min (called arousals). Corresponding BIS was defined for values ≥90. The tendency of a reduced frequency of awakenings under propofol was statistically not significant (Pg median 1.0; Fg median 2.0 [P = 0.163]). By contrast, more arousals were captured after administration of flunitrazepam (Pg median 2.0, Fg median 3.0 [P = 0.041]). All in all, fewer events were registered under injection of propofol (Pg median 3.0, Fg median 5.5 [P = 0.041]). Median duration of every single awakening (hh:mm:ss) was 00:03:22 for Pg and 00:03:30 for Fg (P = 0.424). Altogether, patients receiving propofol spent 00:09:00

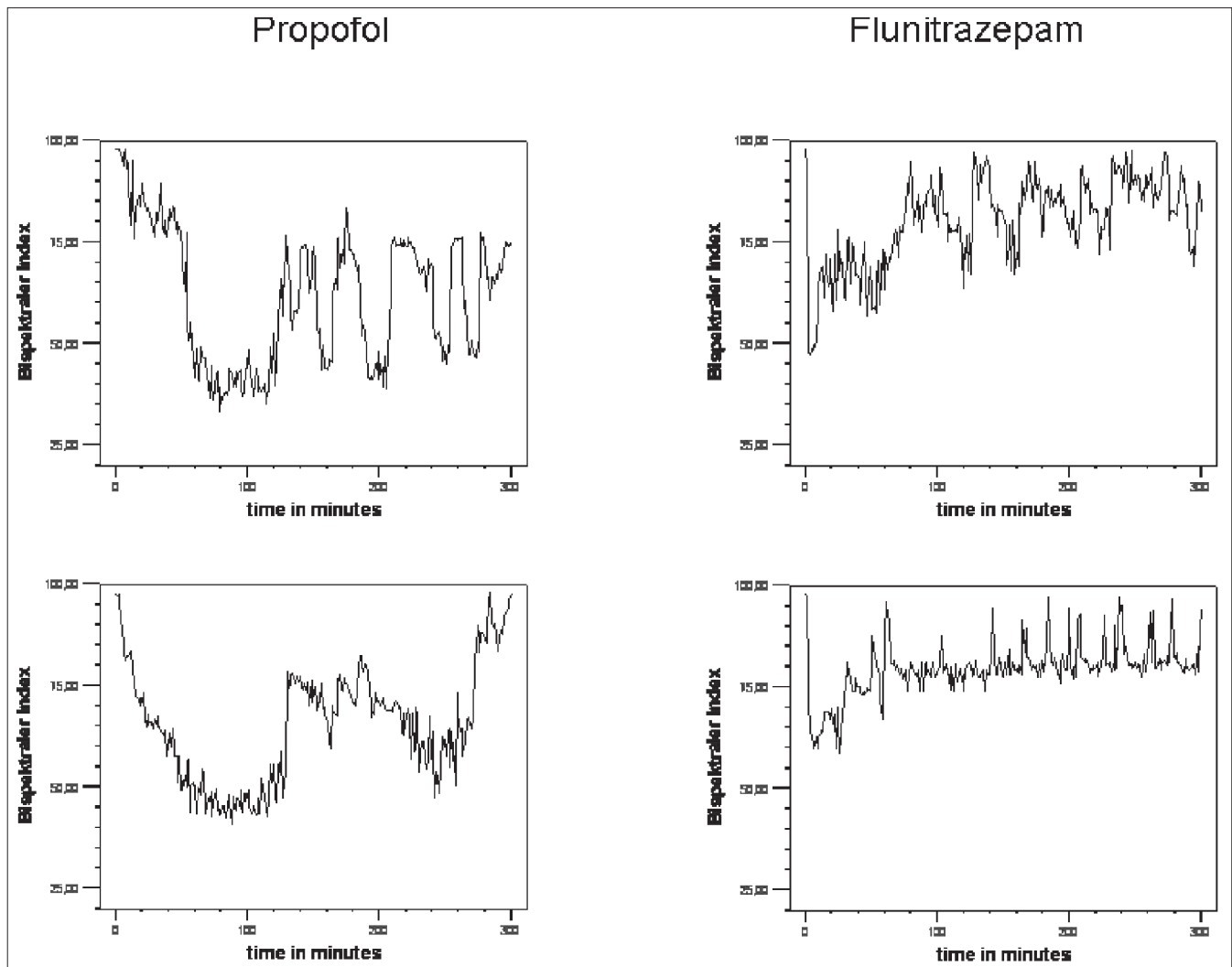


Figure 3: Examples for bispectral index courses over the time (two patients for each group)

Table 3: Distribution of sleep stages and comparison between groups (hh:mm:ss)

Group	Result	Sleep stage			Total sleep time
		C	B	A	
Propofol	Median	0:14:30	1:44:00	2:23:30	4:44:30
	Maximum	2:32:00	4:07:00	4:54:00	5:00:00
	Minimum	0:00:00	0:05:00	0:18:00	1:32:00
Flunitrazepam	Median	0:21:30	2:34:00	1:23:30	4:38:00
	Maximum	4:11:00	4:30:00	4:04:00	5:00:00
	Minimum	0:00:00	0:48:00	0:02:00	0:50:00
Level of significance		P=0.69	P=0.004	P=0.044	P=0.777

The total sleep time comprises sleep stages A and B. Sleep stage A symbolizes deep sleep, sleep stage B light sleep and sleep stage C awake

in a state of awakening or arousal whereas for patients receiving flunitrazepam the corresponding time duration was 00:15:00 ($P = 0.169$).

Correlations

Study population

Under propofol patients reported an increased

frequency of awakenings (sleep diary) with rising age ($r = -0.403 [P = 0.037]$).

Sleep diary

Under the administration of propofol sleep quality worsened as frequency of awakenings increased ($r = 0.489 [P = 0.010]$). In contrast, after flunitrazepam sleep quality decreased as sleep duration shortened ($r = -0.772 [P < 0.000]$). For both drugs, there was a positive correlation between duration of awakenings and sleep quality (Pg $r = 0.599 [P = 0.002]$, Fg $r = 0.497 [P = 0.016]$).

BIS

Interestingly, median BIS values increased with rising duration of awakenings (sleep diary) if propofol was administered ($r = 0.469 [P = 0.024]$). A positive correlation was calculated for sleep quality with the frequency (BIS) ($r = 0.437 [P = 0.023]$) and the duration

of awakenings (BIS) ($r = 0.443$ [$P = 0.021$]). Thus, sleep quality deteriorated with incremental frequency and duration of awakenings (BIS) in Pg.

For both groups median BIS values increased with rising frequency of awakenings (sleep diary) (Pg $r = 0.467$ [$P = 0.019$], Fg $r = 0.564$ [$P = 0.010$]).

Discussion

Maintaining an appropriate sleep-wake cycle is essential for ICU patients.^[4,5,20] Despite its tendency to support light sleep^[21] long acting benzodiazepines like flunitrazepam are generally used for spontaneously breathing and non-sedated patients inducing night sleep. Although propofol favors slow-wave sleep^[13] its benefit for sleep quality in ICU has not been clearly proven.^[16,22] Thus, the current study design has been selected to evaluate the effect of diurnal sedation with propofol regarding night sleep in ICU in comparison with long-acting benzodiazepines as standard of care. Propofol was administered with 2 mg/kg/h that is considerably less than used for maintaining general anesthesia (6-10 mg/kg/h) and patients were continuously monitored for vital signs. As there were no severe complications related to propofol the dose can be regarded as safe in the intensive care setting.

The possible differences of general sleep quality, sleep duration and sleep structure between both groups were assessed by using a standardized sleep diary and the BIS. Since sleep laboratory conditions are too complex to be realized on an ICU and do not reflect the real ICU environment the BIS was selected as an instrument for measuring cerebral activity. The influence on patients' behavior is negligible, technical requirements are low and values can be interpreted easily. The BIS was already evaluated for interpreting naturally occurring sleep.^[18,23]

The used standardized sleep diary^[17] clearly depicted an advantage in sleep quality for patients treated with propofol. The frequency of awakenings (sleep diary) was significantly lower in the Pg. The improved sleep quality observed under propofol compared to flunitrazepam was not realized by increasing sleep duration. More likely these changes were generated by influencing sleep structure and neurohumoral functions. Sleep quality improved under propofol with a decreasing number and duration of awakenings (sleep diary and BIS) and after administration of flunitrazepam with increasing sleep duration (sleep diary).

The BIS median was significantly lower under propofol (Pg 74.05, Fg 78.7 [$P = 0.016$]). The reaction of the BIS within the 1st h was characterized by the different mode of administration. BIS dropped immediately after flunitrazepam administration (median 5.75/min). BIS decreased slowly within the 1st h after the start of propofol injection (median 0.87/min). These differences were not reflected in the patients' assessments. Both groups assessed their quality of falling asleep similarly (median 2). This is probably the result of patients' comparison with often experienced naturally occurring quality of falling asleep at home without medical intervention. Thus, both drugs are assessed as inducing a good quality of falling asleep despite different BIS reactions.

After the 1st h of the study period median BIS values were significantly lower for propofol. Nevertheless, for every individual very different BIS development and a distinct variability was observed which was not typical for pure "sedation-curves" [Figure 3]. After classification of BIS values to sleep stages^[18] patients spent a longer time in slow-wave sleep (NREM stages 3 and 4) under propofol administration. BIS values had to be allocated predominantly to light sleep/REM sleep after application of flunitrazepam. These findings equate to the already known changes in sleep structure after benzodiazepines^[21,24] and under Propofol.^[13] Thus it could be hypothesized that sleep in Pg was dominated by slow-wave sleep and in Fg by light sleep. Naturally, occurring sleep is also characterized by awakenings. Similar to the results of the sleep diary analysis of BIS data revealed a reduced frequency of awakenings in Pg that also correlated well with sleep quality.

However, results of BIS analysis should be interpreted carefully. Haenggi *et al.*^[25] and other study groups revealed that the BIS reaction to different sedation depths depends on the hypnotics used and shows vast variability.^[26-29]

All in all, administration of propofol resulted in decreased BIS values and possibly in a lower frequency of awakenings and arousals as well as an increase in deep sleep compared to sleep after flunitrazepam injection.

Besides different pharmacokinetics of the drugs used in this study some additional limitations have to be mentioned. The overall effect of internal and external influences such as noise, light or the placebo-effect could not be definitively detected. Further studies using polysomnography and a control group (placebo)

should be carried out to clarify possible differences in sleep architecture and awakenings in correlation with sleep quality under sedation with the known drugs. In addition, registrations of disruptive factors have to be correlated to awakenings to rule out environmental factors. Several studies demonstrated that awakenings on ICU could partly be explained by ambient noise.^[1,2,30-32]

Conclusions

In summary, Propofol improved the overall quality of night sleep in ICU patients who were not analgo-sedated or mechanically ventilated compared with flunitrazepam. The observed differences were more likely realized by sleep structural changes than by increasing sleep duration. We found that propofol possibly led to a decreased frequency of awakening and deeper sleep stages. Sleep quality correlated well with the frequency of awakenings in Pg and with sleep duration in Fg. The differences could not be clearly elucidated due to limitations of BIS for assessment of sleep.

These study results should not lead to an uncritical use of propofol for artificial sleep induction as these results refer to a post-operative care population that cannot be extrapolated to ICU patients in general. Furthermore, hypnotics are known, although not observed in this trial, to cause several harmful side-effects which must be avoided. The risk for potential consequences like bronchial aspiration or cardiovascular events is not well-investigated. However, propofol can be an option for ICU-patients who are threatened by complications of sleep deprivation.

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