ORIGINAL

The quality and quantity of sleep on dexmedetomidine during high-flow nasal cannula oxygen therapy in critically ill patients

Yoshitoyo Ueno[1], Koji Sato[1], Kazuki Momota[1], Hiroki Sato[1], Yuki Nakano[1, 2], Yusuke Akimoto[3], Toshiyuki Nunomura[4], Natsuki Tane[3], Taiga Itagaki[4], and Jun Oto[3]

[1]Emergency and Critical Care Medicine, Tokushima University Hospital, 2-50-1, Kuramoto, Tokushima, 770-8503, Japan, [2]Emergency and Critical Care Medicine, Tokushima Prefectural Miyoshi Hospital, 815-2, Ikeda-cho Shima, Miyoshi, 778-8503, Japan, [3]Emergency and Critical Care Medicine, Tokushima University Graduate School of Biomedical Sciences, 3-18-15, Kuramoto, Tokushima, 770-8503, Japan, [4]Emergency and Disaster Medicine, Tokushima University Hospital, 2-50-1, Kuramoto, Tokushima, 770-8503, Japan,

Abstract : Purpose : High-flow nasal cannula oxygen therapy (HFNC) is a new type of non-invasive respiratory support for acute respiratory failure patients. However, patients receiving HFNC often develop sleep disturbances. We therefore examined whether dexmedetomidine could preserve the sleep characteristics in patients who underwent HFNC. Patients and Methods : This was a pilot, randomized controlled study. We assigned critically ill patients treated with HFNC to receive dexmedetomidine (0.2 to 0.7 μg/kg/h, DEX group) or not (non-DEX group) at night (9:00 p.m. to 6:00 a.m.). Polysomnograms were monitored during the study period. The primary outcomes were total sleep time (TST), sleep efficiency and duration of stage 2 non-rapid eye movement (stage N2) sleep. Results : Of the 28 patients who underwent randomization, 24 were included in the final analysis (12 patients per group). Dexmedetomidine increased the TST (369 min vs. 119 min, p=0.024) and sleep efficiency (68% vs. 22%, P=0.024). The duration of stage N2 was increased in the DEX group compared with the non-DEX group, but this finding did not reach statistical significance. The incidences of respiratory depression and hemodynamic instability were similar between the two groups. Conclusions : In critically ill patients who underwent HFNC, dexmedetomidine may optimize the sleep quantity without any adverse events. J. Med. Invest. 69 : 266-272, August, 2022

Keywords **:** *dexmedetomidine, sleep disturbance, high-flow nasal cannula oxygen therapy (HFNC)*

INTRODUCTION

Sleep disturbance is prevalent in intensive-care unit (ICU) patients (1-3). Poor sleep carries a risk of causing physiological and psychological problems, such as an impaired immune function, sympathetic activation, glucose intolerance, prolonged mechanical ventilation or cognitive impairment (1). Sleep in critically ill patients is severely fragmented and shows an abnormal sleep architecture with increased stage 1 (stage N1) and stage 2 (stage N2) non-rapid eye movement (non-REM) sleep and decreased stage 3 (stage N3) and rapid eye movement (REM) sleep (2). ICU patients are commonly exposed to a range of several disturbances, such as a high level of noise and light, tracheal intubation, nursing care, and critical illnesses itself (4). While all of these factors may play a role in the induction of sleep disturbance, the application of less-invasive and comfortable respiratory support may be crucial for maintaining a good sleep quality and quantity in patients with acute respiratory failure (5).

High-flow nasal cannula oxygen therapy (HFNC) is a new type of non-invasive respiratory support for patients with acute hypoxemic respiratory failure (6). This strategy provides good comfort through heated and humidified medical gases with a flow rate of 30 to 60 L/min. Most studies have reported that application of HFNC is associated with greater patient comfort than low-flow oxygen system or non-invasive positive pressure ventilation (NPPV) (7). HFNC shows favorable compliance and tolerance in treating hypoxemic patients due to reduced psychic stress and physical discomfort (6, 7). Therefore, HFNC has been expected to achieve a high sleep quality and quantity in ICU patients. However, previous studies have reported that sleep in patients receiving HFNC in a critical care setting may be impaired due to severe fragmentation of sleep periods by nursing interventions, significant reduction in deep sleep, and the predominance of shallow sleep (8, 9). Anxiety or discomfort associated with nasal cannula, high temperatures and humid gases, noise exposure, and condensation in the nasal prong might be the main causes of sleep disorder in patients treated with HFNC (9-12).

Several strategies have been demonstrated to reduce noise and light, including earplugs, eye masks, white noise, and ocean sounds (13, 14). However, non-pharmacological strategies are not sufficient to prevent sleep disruption, and pharmacological interventions are commonly needed (14, 15). Propofol, benzodiazepines, and opioids are commonly used as a sedative and analgesic medication in the ICU. However, these drugs are suggested to cause adverse effects, such as disruption of sleep architecture, delirium, respiratory depression, and hemodynamic instability (3, 15, 16).

Dexmedetomidine, an α2 adrenoceptor agonist, has been used in ICU patients. Unlike other sedatives, dexmedetomidine applies its sedative effects through an endogenous sleep-prompting pathway and maintains sleep characteristics in mechanically ventilated patients (17, 18). In addition, since dexmedetomidine ensures light sedation, rearousability, and the maintenance of the cognitive brain function without clinically relevant respiratory depression, the U.S Food and Drug Administration (FDA) approves dexmedetomidine for sedation in both intubated and non-intubated patients in the ICU.

Dexmedetomidine may preserve sleep in critically ill patients ; however, its effects on the sleep characteristics in patients

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Address correspondence and reprint requests to Jun Oto, Emergency and Critical Care Medicine, Tokushima University Graduate School of Biomedical Sciences, 3-18-15, Kuramoto, Tokushima, 770-8503, Japan and Fax : +81-88-633-9339. E-mail : joto@tokushima-u.ac.jp

with HFNC remain unclear. We hypothesized that dexmedetomidine infusion would improve the sleep duration and characteristics in critically ill patients with HFNC.

PATIENTS AND METHODS

Study design

This study is a randomized controlled trial conducted in a 11-beds medical- surgical ICU of Tokushima University Hospital between July 2017 and January 2019. The study protocol was approved by the Clinical Research Ethics Committee of Tokushima University Hospital (Institutional Review Board, No.2164) and registered with the Clinical Trial Registry (University hospital Medical Information Network- Clinical Trial Registry : UMIN-CTR, ID 000015650). Written informed consent was obtained from all participating patient or their families.

Patient recruitment

Adult patients who received HFNC and who were anticipated to be in the ICU for at least 24 h were enrolled in this study. Exclusion criteria were the presence of psychiatric illness, a history of sleep disturbance and taking sleep medicine on a daily basis, a history of obstructive sleep apnea syndrome, severe hemodynamic instability with systolic blood pressure < 90 mmHg in spite of vasopressor use, severe renal dysfunction (undergoing dialysis before study) and severe hepatic dysfunction (Child-Pugh class C).

Randomization and study treatment

Eligible patients were randomly assigned to receive dexmedetomidine infusion (DEX group) or not (non-DEX group). Randomization was performed using sealed envelopes and random numbers were assigned in a 1to 1 ratio.

Dexmedetomidine infusion (not preceded by a bolus administration) was started at 0.4 μg/kg/h in the DEX group at 9:00 p.m. and discontinued at 6:00 a.m. Intravenous infusion of dexmedetomidine was followed to maintain a Richmond Agitation Sedation Scale (RASS) of -2 to -1 with a dose of 0.2 to 0.7 μg/kg/h during the study period (19). The attending nursing staff evaluated the RASS at 2- to 4-h intervals or when nursing care was provided. The dosage was up to 0.7 μg/kg/h to suppress patient's agitation. If this strategy was not effective to control agitation, other sedative use was permitted. The administration of other sedatives were decided by the attending physician.

Patients in the non-DEX group received oral sedative drugs, such as ramelteon, suvorexant, or oral benzodiazepines, without dexmedetomidine, if they complained of insomnia. Apparent pain was treated using analgesics targeting a numerical rating scale of ≤ 3. Additional non-pharmacological interventions aimed at promoting sleep, such as minimizing noise, light, and scheduled nursing care, were applied as routine practice. At the end of the study period (6:00 a.m.), we performed an arterial blood gas analysis (ABGA) to evaluate whether respiratory acidosis or hypercapnia due to respiratory depression had occurred.

Polysomnographic monitoring

All patients were monitored with continuous polysomnography (PSG) (Alice PDx ; Phillips Respironics, Murrysville, PA, USA), and sleep data were recorded automatically though the study period (9:00 p.m. to 6:00 a.m.). PSG involved six electroencephalography channels, an electro-oculogram, a chin and bilateral anterior tibial surface electromyogram, a finger pulse oximetry, thoracic and an abdominal movement sensor as an inductance plethysmography, a snoring sensor, and a nasal air-flow sensor. The PSG sleep technicians at the Philips Respironics Sleep Center who were blinded to group assignment later scored polysomnograms in accordance with the 2007 American Academy of Sleep Medicine (AASM) in 30-s epochs (20). Arousal and awakening from sleep were scored in accordance with the AASM manual (21).

We measured the total sleep time (TST), sleep efficiency, percent of each sleep stages (stage N1, N2, N3 and REM sleep), sleep latency, arousal index, apnea-hypopnea index (AHI), 3% oxygen desaturation index (3%ODI), and duration of snoring. TST was defined as the sum of time spent in any sleep stage during the study period. Sleep efficiency was defined as the TST in proportion to the monitoring time. Sleep latency was defined as the time from lights out (9:00 p.m.) to falling asleep. The arousal index was measured as the number of arousals and awakening per hour of sleep. The AHI was measured as the number of apnea and hypopnea incidents per hour of sleep (normal range : <5/h). Because nasal airflow sensors are not reliable during HFNC, the respiratory inductance plethysmography and finger pulse oximetry were used to score apnea and hypopnea events in accordance with the 2007 AASM manual's alternative criteria (21). Apnea is scored when there is a drop in the peak signal excursion by ≥90% of the pre-event baseline using a thoracoabdominal respiratory inductance plethysmography (RIP) belt sensor for ≥10 seconds. Hypopnea is scored when the peak signal excursions drop by ≥30% of the pre-event baseline using a RIP belt sensor for ≥10 seconds in association with either ≥3% arterial oxygen desaturation or arousal. The 3%ODI was calculated as the number of 3% desaturation events per sleep hour (normal range : <5/h). Duration of snoring was expressed as the percentage of TST.

Assessment of adverse events

Delirium was assessed at 2- to 4-h intervals using the confusion assessment methods for the ICU (CAM-ICU) (16). However, we intended to minimize the number of delirium assessments in order to avoid sleep fragmentation if a patient seemed asleep during the study period. Hypotension was defined as a systolic blood pressure <90 mmHg or a decrease of more than 20% from the baseline if the baseline was <113 mmHg. Bradycardia was defined as a heart rate <50 beats/min or a decrease of more than 20% from the baseline if the baseline was <63 beats/min. Hypertension was defined as systolic blood pressure >160 mmHg or an increase of more than 20% from the baseline if the baseline was >133 mmHg. Tachycardia was defined as a heart rate >100 beats/min or an increase of more than 20% from the baseline if the baseline was >89 beats/min (22).

Study outcomes

As primary outcomes, we compared the TST, sleep efficiency, and duration of stage N2 sleep between the two groups. As secondary outcomes, we included other variables that measured by PSG, such as the total amount of each during sleep stage, sleep latency, arousal index, AHI, 3%DSI, and duration of snoring. Adverse events related to sleep disorder or dexmedetomidine infusion during the study period were also evaluated and compared between the two groups.

Statistical analyses

The sample size calculation was based on a previous report that showed that ICU patients requiring mechanical ventilation had their sleep efficiency increased from a median of 16% without sedation to 80% with dexmedetomidine (18). Another study showed that sedation with dexmedetomidine increased sleep efficiency from 11% to 52% compared with no sedation (17). Assuming minimal differences in sleep efficiency between the groups, we assumed that dexmedetomidine would increase sleep

efficiency from 16% to 52% compared to usual care without dexmedetomidine. The standard deviation was estimated to be 24% in both groups, considering the raw data from a previous study (17). The calculation sample size that would provide 90% power to detect this difference based on a 2-tailed significance level of 0.05 was 11 patients per group. Considering a dropout rate about 25%, we intended to enroll 14 patients per group.

An atypical sleep pattern often appears in critically ill patients (23, 24). We therefore excluded such abnormal sleep electroencephalogram (EEG) patterns from the final analysis, as the sleep stage scoring was not reliable. An atypical sleep pattern is defined as follows : an EEG showing a mix of alpha, beta or theta waves and continuous polysomnographic waves (0.5-4 Hz) with a high amplitude (>75 μV) resembling a normal stage N3, but not consistent with normal non-REM sleep because of the absence of typical stage N2 figures (sleep spindles and K-complexes) (23).

Data are presented as median values (interquartile range [IQR]). Data were analyzed using nonparametric tests (SPSS Statistic version 28 ; IBM, Armonk, NY, USA). Variables were compared using the Mann-Whitney-U test. Categorical variables were compared using the Fisher exact test. Statistical tests were two sided, and a $P < 0.05$ was considered statistically significant.

RESULTS

Patient population

General characteristics of the patients are summarized in Table 1. Twenty-eight patients were studied. Three patients did not complete the study due to device intolerance or monitoring failure due to electrode detachment and were thus excluded from the analysis (one in the DEX group and two in the non-DEX group). One patient was excluded from the analysis because PSG showed an atypical sleep pattern ; polymorphic delta activity with alpha or beta activity superimposed on delta waves without sleep spindles and/or K-complexes, and the sleep stage was scored with stage N3 accounting for 70.9% of TST, so the sleep stage scoring was not reliable (DEX group). The final analysis was therefore conducted in 24 patients, including 12 per group, as indicated by the statistical plan.

Baseline variables were comparable between the two groups (Table 1). About half of patients underwent cardiovascular surgery. One patient in the non-DEX group received oral sed-

Table 1. Baseline demographics and characteristics

	Total N = 24	DEX N = 12	non-DEX N = 12	P values
Age (years)	76 (70, 78)	76 (71, 78)	74 (67, 79)	.671
Male/Female (n)	15/9	9/3	6/6	.711
APACHE Ⅱ score	19 (16, 22)	19 (16, 22)	19 (13, 22)	.551
BMI (kg/m^2)	24 (21, 26)	24 (23, 26)	24 (20, 26)	.843
Type of ICU admission n (%)				
Medical	11 (45.8)	7 (58.3)	6(50)	1.00
Surgical	13 (54.2)	5 (41.7)	6 (50)	1.00
Days in ICU before enrollment	2 (2, 3)	3 (2, 3)	2 (2, 2)	.160
Admission diagnosis n (%)				
Cardiovascular surgery	11 (45.8)	5 (41.7)	6 (50)	1.00
Acute respiratory failure	5 (20.8)	3 (25)	2 (16.7)	1.00
Congestive heart failure	3 (12.5)	2 (16.7)	1 (8.3)	1.00
Acute myocardial infarction	2 (8.3)	0 (0)	2 (16.7)	.478
Others	3 (12.5)	2 (16.7)	1 (8.3)	1.00
Comorbidity n (%)				
Hypertension	11 (45.8)	6 (50)	5 (41.7)	1.00
Coronary heart disease	5 (20.8)	3 (25)	2 (16.7)	1.00
Diabetes mellitus	7 (29.2)	5 (41.7)	2 (16.7)	.371
COPD	1 (4.2)	0 (0)	1 (8.3)	1.00
Renal dysfunction	3 (12.5)	2 (16.7)	1 (8.3)	1.00
HFNC setting				
Flow (L/min)	40 (40, 40)	40 (40, 40)	40 (38, 40)	.755
F_IO_2	0.3 (0.29, 0.36)	0.3 (0.29, 0.46)	0.3 (0.29, 0.31)	.551
Other sedative use n (%)				
Ramelteon and suvorexant	1 (4.2)	0 (0)	1 (8.3)	1.00
Catecholamine use n (%)	9 (37.5)	2 (16.7)	7 (58.3)	.089
Steroid use n (%)	8 (33.3)	6 (50)	2 (16.7)	.193
Duration of PSG recording (h)	9 (9, 9)	9 (9, 9)	9 (9, 9)	1.00

Data are presented as the median [IQR, interquartile range] or n (%) unless otherwise noted.
APACHE, acute physiologic and chronic health evaluation score ; BMI, Body Mass Index ; ICU, intensive-care unit ; COPD, chronic obstructive pulmonary disease ; PSG, polysomnography.

atives, ramelteon and suvorexant, due to insomnia during the study period. The HFNC settings were a flow of about 40 L/min and F_IO_2 of about 0.3 in both groups. The percentages of steroid use and catecholamine use were not markedly different between the groups.

Sleep architecture analyses

Table 2 and Figure summarizes the sleep data. Analyses of polysomnograms in the non-DEX group showed a shortened TST, increased percentage of stage N1 and N2, decreased percentage of stage N3 and REM sleep, and high arousal index. The DEX group showed an increased TST, with a median 119 min (IQR, 44, 314) in the non-DEX group and 369 min (IQR, 272, 406) in the DEX group (P=0.024). Sleep efficiency was about 22% in the non-DEX group and 68% in the DEX group (P=0.024). Stages N1 and N2 were predominant, and stage N3 was only detected in two patients in the DEX group. REM sleep was only detected in two patients in the DEX group and one patient in the non-DEX group. Although the percentage of stage N1 during the study period was not markedly different between the groups, the duration of stage N1 was longer in the DEX group than in the non-DEX group (97 min vs. 34 min, P=0.014). The duration of N2 sleep was longer in the DEX group than in the non-DEX group ; however, this finding did not reach statistical significance (252 min vs. 48 min, P=0.143) (Figure). The arousal index was lower in the DEX group than in the non-DEX group, but without statistical significance (21.2/h vs. 37.0/h, p=0.16).

Additional endpoints

The median RASS level did not differ markedly between the two groups, and a target RASS level -1/-2 was reached in 83% of patients in each group. With regard to respiratory parameters, there was no significant difference in values of the AHI, 3%ODI, duration of snoring, or ABGA data (pH, $PaCO_2$) between the two groups (Table 2). Delirium occurred in 1 patient (8.3%) per group. There were no significant differences between the two

Table 2. Outcomes during the period of ICU admission.

	Total N = 24	DEX N = 12	non-DEX N = 12	P values
Primary endpoint				
Total sleep time (min)	288 (129, 402)	369 (272, 406)	119 (44, 314)	**.024**
Sleep efficiency (%)	53 (24, 75)	68 (50, 75)	22 (8, 58)	**.024**
Secondary endpoint				
Duration of Stage N1 sleep (min)	68 (35, 110)	97 (75, 114)	34 (13, 52)	**.014**
Percentage of stage N1 sleep (%TST)	31 (20, 61)	28 (20, 41)	44 (19, 82)	.551
Duration of Stage N2 sleep (min)	174 (27, 303)	252 (147, 309)	48 (10, 220)	.143
Percentage of stage N2 sleep (%TST)	65 (39, 80)	69 (59, 80)	55 (18, 81)	.478
Duration of Stage N3 sleep (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.514
Percentage of stage N3 sleep (%TST)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.514
Duration of REM sleep (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.799
Arousal index (n/h)	29.0 (15.9, 37.4)	21.2 (15.9, 34.0)	37.0 (21.1, 53.0)	.160
AHI (n/h)	0.5 (0, 3.0)	0.4 (0.2, 1.2)	2.5 (0, 3.5)	.590
3%ODI (n/h)	1.9 (0.1, 12.3)	1.9 (0.9, 19.6)	0.7 (0, 9.4)	.478
Duration of snoring (%TST)	0 (0, 0)	0 (0, 0.1)	0 (0, 0)	.797
Exploratory analysis				
Presence of Stage N3 sleep n (%)	2 (8.3)	2 (16.7)	0 (0)	.478
Presence of REM sleep n (%)	3 (12.5)	2 (16.7)	1 (8.3)	1.00
Sleep latency (min)	33 (13, 60)	43 (13, 58)	31 (21, 64)	.799
RASS	-1 (-1, -1)	-1 (-1, -1.3)	-1 (-1, -1)	.41
RASS target -1/-2 n (%)	20 (83.3)	10 (83.3)	10 (83.3)	1.0
Delirium n (%)	2 (8.3)	1 (8.3)	1 (8.3)	1.0
Dexmedetomidine dose (μg/kg/h)		0.41 (0.3, 0.46)	0	
pH	7.48 (7.45, 7.51)	7.51 (7.47, 7.51)	7.47 (7.45, 7.49)	.178
$PaCO_2$ (mmHg)	35 (30, 40)	35 (30, 40)	35 (32, 39)	.887
Hypotension n (%)	1 (4.2)	1 (8.3)	0 (0, 0)	1.00
Bradycardia n (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1.00
Hypertension n (%)	4 (16.6)	1(8.3)	3 (24.5)	.59
Tachycardia n (%)	2 (8.3)	0 (0, 0)	2 (16.7)	.48
Intervention for hypertension n (%)	3 (12.5)	0 (0, 0)	3 (24.5)	.217
Length of ICU stay (days)	6 (4.8, 8)	7 (5, 8)	5 (4, 7)	.319

Data are presented as the median [IQR, interquartile range] or n (%) unless otherwise noted.
N1, N2, N3, Non-Rapid Eye Movement stages ; REM, Rapid Eye Movement ; AHI, Apnea-Hypopnea Index ; ODI, Oxygen Desaturation Index ; RASS, Richmond Agitation-Sedation Scale ; $PaCO_2$, Partial Pressure of Carbon Dioxide ; ICU, intensive-care unit.

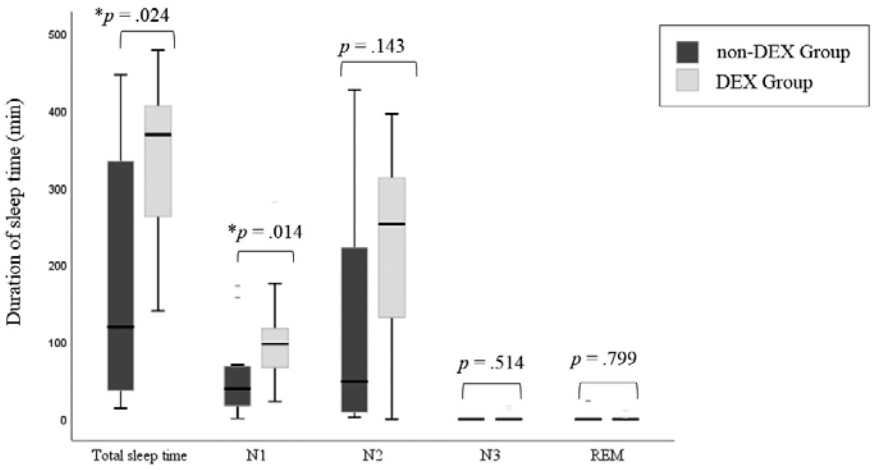

Figure. Duration of total sleep time and sleep stages in each group.
The box plots showing the median and interquartile range for the total sleep time and duration of stages N1-3 and REM sleep at night (9:00 p.m. to 6:00 a.m.).
*Significant difference between the two groups.

groups with regard to the incidence of hemodynamic instability (hypotension, bradycardia) and rate of patients receiving intervention for any adverse events (Table 2).

DISCUSSION

This study showed that, among ICU patients who received HFNC, dexmedetomidine increased the total sleep time and sleep efficiency without any adverse events, such as respiratory depression or hemodynamic instability. To our knowledge, this is the first study to evaluate the effects of dexmedetomidine on the sleep quality and quantity in patients with HFNC in the critical care setting. This study demonstrated that the sleep characteristics of ICU patients with HFNC manifested as a shortened total sleep time, decreased sleep efficiency, frequent arousal and awakening, abnormally increased percentage of stage N1 and N2, and decreased stage N3 sleep and REM sleep compared with the structure of normal sleep in old-age healthy individuals (25). These results were similar to the polysomnographic data reported in patients with invasive and non-invasive mechanical ventilation in the ICU (17, 18, 24).

Associated with lower morbidity and mortality than NPPV, HFNC is being used increasingly frequently as an alternative means of non-invasive respiratory support for acute hypoxemic respiratory failure (6). HFNC shows favorable compliance and tolerance in treating hypoxemic respiratory failure because of reduced psychic stress and physical discomfort (6, 7). Therefore, HFNC may be expected to achieve a high sleep quality and quantity in ICU patients.

However, patients in the non-DEX group showed a median sleep efficiency during the study period of only 22%. Meyer *et al*. reported that HFNC did not correct the sleep quality or quantity compared with no treatment or NPPV for sleep-related disorder breathing in patients with neuromuscular disease (8). In their study, the median sleep efficiency was 55.9%, and the 91% TST was predominantly occupied by shallow sleep of stage N1 and N2 at an HFNC flow rate of 50 L/min. In addition, HFNC at a high flow rate of 40 to 60 L/min was poorly tolerated (8, 26, 27). Anxiety and discomfort associated with nasal cannula, a high flow and high temperature of humid gases, noise exposure, and condensation that accumulated in the nasal prong and spraying into patient's nostril may all disrupt a patient's sleep (9-12). To improve sleep the quality and quantity during HFNC, it may be crucial to optimize the HFNC flow and temperature settings and to avoid a low ambient temperature (<25 °C) in order to minimize noise exposure, condensation in the circuit, and patient discomfort (12, 28).

Dexmedetomidine exerts its sedative effects through an endogenous sleep-promoting pathway and preserves the sleep architecture to some degree in the clinical setting. In previous studies, it was reported that dexmedetomidine produces EEG spindle and slow delta oscillation that resembles N2 sleep and increases the sleep efficiency and duration of N2 sleep (17, 18, 22). Our study showed that dexmedetomidine increased the TST and sleep efficiency but not the proportion or duration of stage N2 sleep during the study period (DEX group vs. Non-DEX group : 69% vs. 55%, P=0.478 ; 252 min vs. 48 min, P=0.143). This is likely because the sample size of this study (12 patients per group) was relatively small and not large enough to detect difference between the two groups. Romagnoli *et al*. performed an observational study with a sample size of 36 patients per group to evaluate sleep characteristics in non-mechanically ventilated patients in the ICU with and without dexmedetomidine infusion. They reported that dexmedetomidine infusion increased sleep efficiency from a median 48% without dexmedetomidine to 84% with dexmedetomidine and increased the percentage of stage N2 sleep from 50% without dexmedetomidine to 69% with dexmedetomidine (29). These values were likely similar to our own data.

In both groups, the median RASS was -1 (IQR : -1, -1), which indicated a shallow sleep status, and the target RASS value of -1/-2 was achieved in 83% of patients. However, there was a significant difference in the TST and sleep efficiency between the two groups. One possible reason was that there is a large discrepancy between the subjective sleep observation and PSG evaluation. Sleep time as estimated by nursing staff was often entirely misjudged and consistently overestimated compared with the paralleled polysomnographic recordings (30, 31). Indeed, Aurell *et al*. reported that even when sleep time estimated by nursing staff showed about 7 h, sleep time as measured by paralleled PSG was only about 2.5 h (31).

It is well recognized that many sedatives impair the central

and peripheral regulation of breathing and decrease the muscle tone of the upper respiratory tract, which may cause apnea and upper airway obstruction (16, 32). Lodenius *et al*. reported that a sedative dose of dexmedetomidine (median loading dose of 0.59 μg/kg for 10 min followed by an infusion of 0.53 μg/kg/h) reduces ventilatory responses to hypoxia and hypercapnia to a similar extent as sedation with propofol (median loading dose of 74.5 μg/kg for 10 min followed by an infusion of 48.6 μg/kg/min) in healthy volunteers (32). In addition, dexmedetomidine-induced sedation causes upper airway obstruction and episodes of apnea to the same degree as propofol-induced sedation (32). Our study showed that there were no significant differences in respiratory parameters, such as the AHI, 3%ODI, or duration of snoring and ABGA (pH, $PaCO_2$), between the two groups, and all of these parameters were within normal ranges. These results were consistent with the polysomnographic data in extubated spontaneous breathing post-surgical patients with dexmedetomidine sedation (22). In addition, we did not use a loading dose of dexmedetomidine to avoid respiratory or hemodynamic adverse responses. Given the above, dexmedetomidine infusion without loading dose appears to have no clinically important adverse effects on respiration in patients with HFNC.

Despite increasing sleep efficiency by dexmedetomidine infusion, the arousal index was not decreased by treatment in our patients (DEX group vs. non-DEX group ; 21.2/h vs. 37.0/h, p=0.16). This is likely because the sample size of this study was too small to detect differences between the two groups. Alternatively, sedation with dexmedetomidine is characterized by rapid arousal in response to verbal, tactile, or painful stimuli, all of which are common in the ICU environment, with a return to sedation soon after cessation of stimulation (33, 34). In addition, dexmedetomidine preserves the cognitive function during light to moderate sedation and reduces the incidence of delirium compared with benzodiazepine (35). In our study, the rate of delirium was not markedly different between the two groups.

Several limitations associated with the present study warrant mention. First, we did not perform a baseline sleep study before ICU admission. Therefore, we cannot exclude the potential bias induced by the imbalance of baseline sleep characteristics in the two groups. We excluded patients with a history of sleep deprivation and obstructive-sleep apnea syndrome, which may have helped reduce this bias between the two groups. Second, we performed polysomnographic recording for only one night and were not able to evaluate any long-term effects of dexmedetomidine. Third, the sample size was too small to allow for a logistic regression analysis, and factors that may have confounded the results were not excluded. In addition, we did not evaluate the ICU environment factors, such as noise, light and number of nursing-care interactions, which may have affected the sleep characteristics.

In conclusion, our study demonstrated that the sleep characteristics of ICU patients who received HFNC manifested as a shortened TST, frequent arousal and awakening, and abnormally increased percentage of stage N1 and N2 sleep and decreased stage N3 and REM sleep. Nighttime dexmedetomidine infusion effectively increased the TST and improved sleep efficiency without any adverse events, such as respiratory depression or hemodynamic instability. Further studies with larger sample sizes are warranted to evaluate the impact of dexmedetomidine on the sleep quality and consequences of sleep disturbance on the outcomes of patients with HFNC.

CONFLICT OF INTERESTS

All authors have no conflict of interests.

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