Sleep in Critically Ill Chemically Paralyzed Patients Requiring Mechanical Ventilation

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Sleep in Critically Ill Chemically Paralyzed Patients Requiring Mechanical Ventilation*

Kimberly A. Hardin, MD, MS, FCCP; Masud Seyal, MD, PhD; Ted Stewart, MS, RPSGT; and H. William Bonekat, DO

Objective: To determine sleep characteristics in patients receiving mechanical ventilation who require a neuromuscular blocking agent (NMBA).

Design: Observational study.

Setting: Adult medical ICU at a university hospital.

Participants: Eighteen patients with respiratory failure requiring mechanical ventilation were classified into three groups based on medication regimen determined *a priori*: intermittent sedation (IS), continuous sedation (CS), or CS and an NMBA.

Measurements: Twenty-four-hour polysomnography was performed to determine sleep architecture and fragmentation. Measurement of severity of illness, laboratory indexes, patient-care interventions, and drug dosage were compared between groups, and the effects on sleep staging and fragmentation were analyzed. Sleep stages were scored manually using criteria of Rechtschaffen and Kales, as well as by a modified 50-μV voltage criteria for scoring delta activity.

Results: All patients demonstrated abnormal sleep architecture. In each group of patients, the total sleep time (TST) was >10 h. There was no statistical difference in the delta activity between the two scoring methods; delta activity was increased in all groups: 32.9%, 49.6%, and 43.7% in the IS, CS, and CS/NMBA groups, respectively. Patients receiving NMBA spent 22% of the sleep period awake. Rapid eye movement sleep could not be detected in the patients receiving NMBA and was reduced in the other two groups (3.5%). TST, sleep stage, or arousal/awakening index were not statistically correlated with either severity of illness, clinical laboratory indexes, drug dosage, patient-care interventions, or mode of mechanical ventilation.

Conclusion: TST during a 24-h period is not reduced in patients requiring mechanical ventilation. Delta activity is increased and may reflect age, drug, or a contributing metabolic process. The effect of wakefulness in patients receiving chemical paralysis on recovery and weaning from mechanical ventilation, and overall clinical outcome is unknown. (CHEST 2006; 129:1468–1477)

Key words: ICU; mechanical ventilation; polysomnography; sleep

Abbreviations: APACHE = acute physiology and chronic health evaluation; CS = continuous sedation; EOG = electro-oculogram; IL = interleukin; IMV = intermittent mandatory ventilation; IS = intermittent sedation; LIS = lung injury score; mDelta = modified delta; NMBA = neuromuscular blocking agent; PS = pressure support; REM = rapid eye movement; SIMV = synchronized intermittent mandatory ventilation; SWS = slow-wave sleep; TNF = tumor necrosis factor; TST = total sleep time

Sleep deprivation is a well-documented problem among patients in the ICU and may impair physiologic and psychological well-being. Initial investigations using polysomnography reveal decreased total sleep time (TST), as well as abnormal sleep architecture with increased stage 1 and stage 2 non-rapid eye movement sleep, decreased slow wave...
sleep (SWS), and decreased rapid eye movement (REM) sleep.¹⁻³ However, these studies are limited to only 8-h nighttime data collection and excluded patients receiving mechanical ventilation.

Twenty-four–hour polysomnography in ICU patients receiving mechanical ventilation demonstrated inconsistent results in TST and sleep architecture.⁴⁻⁸ Cooper and coworkers⁷ report a subset of patients with > 50% delta activity and considered this to be “unidentifiable electrophysiologic sleep” consistent with encephalopathy or coma, although no specific source for encephalopathy could be determined. Gabor and colleagues,⁸ in contrast to prior ICU studies, determined REM sleep time (14.3%) to be normal.

The etiology of sleep disruption in critically ill patients requiring mechanical ventilation is multifactorial.⁸⁻¹³ Sleep deprivation can have significant consequences and has been shown to impair cognitive function, increase protein catabolism, decrease immune function, and alter respiratory mechanics that could negatively impact tolerance to and weaning from mechanical ventilation.¹,³,¹⁴⁻¹⁹

Neuromuscular blocking agents (NMBAs) are necessary at times to facilitate mechanical ventilation.²⁰ Although anxiolytic medications are routinely administered, patients have reported feeling “buried alive,” have recollection of events, and complain of poor sleep while receiving mechanical ventilation and/or NMBAs.²¹⁻²³ Previous sleep investigations have not included patients receiving NMBAs, and their effect on sleep patterns is unknown. Accurate and objective monitoring of sleep is necessary in patients receiving NMBAs in whom visual and behavioral evidence of their sleep state is lost. Additionally, sleep data are limited in the severely ill ICU patient population requiring mechanical ventilation.

We hypothesized that patients requiring NMBAs would have severely disrupted sleep architecture and would be oversedated due to the loss of visual evidence of sleep/wake state resulting in excessive delta activity. The aims of our study were as follows: (1) substantiate and add to the limited information on 24-h sleep patterns in critically ill patients receiving mechanical ventilation; (2) determine if NMBAs have an effect on sleep patterns; and (3) evaluate the effects of sedation dosage, severity of illness scores, and other clinical indexes on sleep architecture.

Materials and Methods

Study Site

The study was performed between June 1, 1999, and December 31, 2000, in the adult medical ICU at the University of California, Davis. The study protocol and consent form were approved by the Institutional Review Board of the Human Subjects Committee. Written informed consent was obtained from the patient or family member if the patient had any altered sensorium or was unable to read or write. All patients were in private rooms that were enclosed on three sides and separated from the nursing station and equipment room by a sliding glass door. All rooms had windows and were similarly located with respect to external noise sources.

Patient Selection

Three groups of patients (n = 6 per group) with respiratory failure were prospectively studied to discriminate the effects of sedation, narcotics, and NMBAs on polysomnographic results. Patients were screened for eligibility to the study within 48 h of hospital admission. Inclusion criteria required intubation within 24 h of admission, anticipated mechanical ventilation for > 48 h, and a medication regimen set a priori into one of the following three categories: group 1 (intermittent sedation [IS]), consisting of patients who received only IS or pain medication. These patients were fully awake, alert, and able to follow commands. Group 2 (continuous sedation [CS]) consisted of patients who were receiving IV CS without any paralytic agent. Group 3 (CS/NMBA) consisted of patients who received both IV CS and an NMBA.

Exclusion criteria for all groups were the presence of head trauma, psychiatric illness (including use of antidepressant medications), axonic brain injury, suspected encephalopathy (drug overdose, hepatic failure), seizure disorder, and severe hemodynamic instability in whom systolic BP was < 90 mm Hg despite vasopressor support. Oxygen saturation levels were > 90% in all patients. All patient-care treatment decisions, including assignment to IS, CS, and CS/NMBA groups, were determined by the critical care attending physician and were not altered by any investigator during the study.

Polysomnography and Scoring

All subjects were monitored continuously for 24 h using polysomnography recorded on an eight-channel, portable EEG device (Neurotrac II model M1283A; Telefactor; Philadelphia, PA) interfaced with a monitor (model M1064B; Hewlett-Packard; Andover, MA). Gold cup electrode placement was performed according to the international 10/20 system in the following montage: O1-F7, O2-F8, T3-Cz, C3-A2, C4-A1, four electrooculogram (EOG) electrodes were applied for determin- ing vertical and horizontal eye movement, and two chin elec-trodes were placed.²⁴ Electrode application was performed by one trained nurse (L.M.) and the author (K.A.H.). Electrode impedance was maintained at < 10,000 ohms.

Data were archived on an external hard drive for later analysis with customized software on a standard personal computer. Sleep recordings were scored manually in 30-s epochs by a registered polysomnography sleep technician (blinded to patient group) using standard Rechtschaffen and Kales criteria.²⁴ Epochs with delta frequency that did not meet the 75-μV criteria or stage 1 or 2 requirements were scored as nonclassifiable. To account for an expected decrease in amplitude of delta waves associated with aging, a modified delta (mDelta) criteria was also used and consisted of a frequency criterion of < 4 Hz and an amplitude criterion of > 50 μV (peak to peak).²⁵⁻²⁶

TST was defined as the sum of total time spent in all sleep stages during the total time monitored (sleep period). The percentage of time spent in each stage of sleep during the TST was calculated. This was further separated into daytime and nighttime sleep periods. The daytime period was defined as 6 AM
until 10 PM, and the nighttime period was defined 10 PM to 6 AM. The number of arousals per TST and awakenings per TST were compared between each group to evaluate sleep fragmentation. Arousals were defined as an abrupt change in the EEG frequency to α, θ, or frequencies > 12 Hz lasting ≥ 3 s.27 Awakenings were defined as changes in the EEG compatible with wakefulness that lasted > 15 s of an epoch preceded and followed by an epoch of sleep.

**Data Collection**

Recordings were conducted continuously over 24 h to allow assessment of circadian variation. Day and night cycles were simulated by turning patient room lights off at 10 PM. The staff were instructed to record the time and length of all activities, vital signs, medications, nursing care, procedures, and medical examinations on a bedside log sheet. The number of interventions was compared between the three groups.

The NMBA administered was vecuronium by continuous infusion and titrated using the Dulin-Williams standard train-of-four protocol.28 The anxiolytic medication lorazepam was administered for sedation and titrated to a Ramsey score of 3 to 4.29 Morphine sulfate was administered intermittently or by continuous infusion for analgesia. All medication doses were recorded.

Data were collected from the patients’ record for severity of illness, admitting diagnosis, microbiology culture results, and laboratory chemistry. Severity of illness was measured by the calculated APACHE (acute physiology and chronic health evaluation) II score and the lung injury score (LIS).30,31

**Statistical Analysis**

Nonparametric analysis of variance (Kruskal-Wallis) test was used to detect a statistical difference between all three groups. The Dunn multiple comparison test was utilized to detect differences between groups. The Mann-Whitney rank-sum test was used to confirm intergroup results. Pearson correlation coefficient and linear regression (data were log transformed) were used to evaluate the association between APACHE II score, LIS, drug dosage, and TST and individual sleep stage, as well as the relationship between arousal and awakening scores and interventions (including mode of mechanical ventilation). Statistical analysis was performed by a statistician (SAS System Version 8; SAS Institute; Cary, NC).

**RESULTS**

**Patient Demographics**

A total of 20 patients were enrolled in the study. Eighteen patients underwent final analysis. One patient withdrew from the study after consent was obtained. The recorder malfunctioned during data acquisition in another patient. The study population characteristics are given in Table 1. Overall, ages ranged from 27 to 74 years with a younger population in the CS group (p < 0.02). When the one outlier, a 27-year-old patient, was eliminated from age analysis, no statistical difference existed between the groups. The IS and CS groups had more women than men, whereas the CS/NMBA group had almost all men. There was no correlation between age and TST or any stage of sleep. The majority of all patients were admitted for pneumonia. Concomitant diagnoses were present in all groups (COPD and pneumonia), and therefore the total number of diagnoses does not equal 18. In the CS/NMBA group, ARDS was present in five of six patients.

**Table 1—Demographic Data**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IS Group</th>
<th>CS Group</th>
<th>CS/NMBA Group</th>
<th>All Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58.5 ± 9.8</td>
<td>43.2 ± 13</td>
<td>61.3 ± 8.8</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>1/5</td>
<td>2/4</td>
<td>5/1</td>
<td>8/10</td>
</tr>
<tr>
<td>ICU days</td>
<td>2.6 ± 0.8</td>
<td>5.5 ± 2.5</td>
<td>3.6 ± 2</td>
<td>3.9 ± 2</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>79 ± 10</td>
<td>88 ± 32</td>
<td>69.9 ± 5</td>
<td>78.9 ± 20</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>104 ± 20</td>
<td>110 ± 14</td>
<td>102 ± 17</td>
<td>10.5 ± 17</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.4 ± 0.6</td>
<td>37.2 ± 0.6</td>
<td>37.6 ± 0.8</td>
<td>37.4 ± 0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57.1 ± 14</td>
<td>83.4 ± 26</td>
<td>82.3 ± 15</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>APACHE II score†</td>
<td>11.5 ± 3.3</td>
<td>16.5 ± 7.7</td>
<td>22.1 ± 9.9</td>
<td>16.7 ± 8</td>
</tr>
<tr>
<td>LIS‡</td>
<td>0.81 ± 0.6</td>
<td>1.46 ± 0.45</td>
<td>2.9 ± 1.14</td>
<td>1.7 ± 1</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>4 (66)</td>
<td>10 (55)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>0</td>
<td>1 (16)</td>
<td>2 (33)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (33)</td>
<td>1 (16)</td>
<td>1 (16)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>1 (16)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1 (16)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>ARDS</td>
<td>0</td>
<td>1 (16)</td>
<td>5 (83)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Positive culture results</td>
<td>3 (50)</td>
<td>5 (66)</td>
<td>2 (33)</td>
<td>10 (55)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>0</td>
<td>1 (16)</td>
<td>3 (50)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (16)</td>
<td>3 (50)</td>
<td>4 (22)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%) unless otherwise noted.
†On day of study.
‡Significant difference between IS and CS/NMBA groups, p < 0.016.
§Significant difference between IS and CS/NMBA groups, p < 0.016.
Severity of Illness, Clinical and Laboratory Indexes Between Groups

A nonsignificant trend (p = 0.07) of increasing severity of illness (APACHE II), greatest in the CS/NMBA group relative to the IS group, was noted. The LIS was significantly higher in the CS and CS/NMBA groups (p < 0.001) than in the IS group. The LIS in the CS/NMBA group was 50% greater than in the CS group (p < 0.016; Table 1). There was no significant difference between the groups regarding length of stay in the ICU prior to the day of study, and no correlation existed between length of stay and sleep data. Use of vasopressor drugs was greatest in the CS/NMBA group, of whom 50% required hemodynamic support.

Mode of mechanical ventilation varied between the groups. None of our patients were receiving assist-control ventilation. Pressure support (PS) ventilation was used throughout the entire 24-h period in only 2 of the 18 patients: 1 patient in the IS group and 1 patient in the CS group. Volume control using synchronized intermittent mandatory ventilation (SIMV) was used in five patients in the IS group (of whom four were changed during the 24 period to PS mode), four patients in the CS group, and three patients in the CS/NMBA group. Pressure control/intermittent mandatory ventilation (IMV) mode was used in five patients in the CS/NMBA group and one patient in the CS group. Patients receiving pressure control ventilation required vasopressor therapy and had higher APACHE II scores.

Blood cultures were obtained in 17 patients (none in the patient with amyotrophic lateral sclerosis), but results were positive (fungus) in only 1 patient. Tracheal aspirate or BAL findings were positive in seven patients, and open lung biopsy was positive in one patient. Total positive culture results were distributed among the groups as follows: three patients, five patients, and one patient in the IS, CS, and CS/NMBA groups, respectively. Total bilirubin was elevated in one patient in the IS group (3.2 mg/dL) and one patient (3.4 mg/dL) in the CS/NMBA group (data not shown). Renal insufficiency, defined as a serum creatinine level > 2 mg/dL, was present in three patients receiving IS and in only one patient (2.2 mg/dL) in the CS group.

Drug Dosage Between Groups

Drug dosage was compared using both absolute dosage and dose per body weight. There was no statistical difference in body weight between groups (p = 0.06). However, there was an observed lower body weight in the IS group compared to the other two groups (Table 1). Drug dosage differed significantly between the groups (Table 2). Patients in the CS group received the largest amount of sedation and narcotics. Patients in the CS/NMBA group received the least amount of narcotics. There was no statistically significant difference in sedation dose between the CS and CS/NMBA groups. Patients in the IS group were fully alert and able to request pain medication and received the least amount of both sedatives and narcotics. Four patients received sedation, and three of these patients received morphine concomitantly. The other two patients did not receive any drugs. In the CS group, all patients received both morphine and sedation. In the CS/NMBA group, only three patients received morphine in addition to CS. One patient in the CS group received haloperidol for agitation.

Sleep Architecture

Sleep Stages Between Groups: All patients demonstrated abnormal sleep architecture by lack of sequential progression through sleep stages and abnormal distribution of sleep stage quantities compared with standard normative values. TST was increased in all groups compared to normative age-adjusted values. A nonsignificant trend (p = 0.06) of increasing TST, greatest in the CS/NMBA groups relative to the IS group, was noted (Table 3). Greater than 55% of the 24-h TST occurred during the daytime period in all groups (data not shown).

A large variation in the quantity of each specific sleep stage occurred within each group and is reflected by the wide SD (Table 3). Stage 1 was increased only in the CS group. Stage 2 sleep was decreased in the CS group, and a wide variability (0.29 to 91%) existed. The standard Rechtschaffen and Kales delta activity was 31.9%, 48.9%, and 38.9% compared to mDelta activity of 32.9%, 49.6%, and 43.7% in the IS, CS, and CS/NMBA groups, respectively. Delta activity scored by either method was higher than published normative data (0 to 13%). There was no statistical difference in delta

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Table 2—Drug Dosages per Group

<table>
<thead>
<tr>
<th>Drug</th>
<th>IS Group</th>
<th>CS Group</th>
<th>CS/NMBA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.04 ± 0.04</td>
<td>0.72 ± 0.39</td>
<td>0.62 ± 0.20</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Morphone</td>
<td>4.4</td>
<td>58.5</td>
<td>52.3</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD unless otherwise noted.
†Significant difference between IS and CS groups.
‡Significant difference between IS and CS/NMBA groups.
§Significant difference between CS and CS/NMBA groups.
activity for staging slow-wave sleep (SWS) between the two methods \((p = 0.96)\). The Rechtschaffen and Kales scoring criteria resulted in 0%, 1%, and 5% reductions in staging SWS in the IS, CS, and CS/NMBA groups, respectively. Further results are reported using the mDelta data. Fifty percent of the subjects in the CS group had \(> 80\%\) mDelta activity, and the other 50% had \(< 8\%\) mDelta. In the group receiving NMBA, only two subjects had \(< 30\%\) mDelta activity. In the IS group, only one patient had \(> 30\%\) mDelta activity that was also associated with superimposed alpha activity. This patient had the highest LIS, sedation, and narcotic dosage in the IS group.

REM sleep was severely diminished in the IS group (3.6% TST) [Table 3]. Data were not analyzed further, as only 50% of patients receiving CS had detectable REM and no REM was detectable in the patients receiving NMBA.

Sleep Fragmentation: Arousals and Awakening Between Groups: Twenty-four–hour sleep efficiency was increased in all groups (data not shown), but the 8-h nocturnal sleep efficiency was 40%, 49%, and 70% in the IS, CS, and CS/NMBA groups, respectively. This indicates a substantial proportion of sleep occurred during the daytime. The CS and CS/NMBA groups had less wake time than the IS group (Table 3). Patients receiving NMBA spent 22% of the sleep period awake. There was an increasing trend in the arousal index and awakenings in the CS/NMBA group; however, there was no statistical difference between groups (Table 3) or when compared to normative values \((10/\text{h})\). The number of patient-care interventions differed between the groups (Table 3). Patients in the IS group had fewer interventions than the CS/NMBA group, and there was a trend with increasing interventions in the CS/NMBA group compared to the CS group \((p = 0.06)\). However, there was no correlation between the total number of interventions per patient in each group with the number of arousals or awakenings per patient.

**Correlation With Severity of Illness Scores, and Clinical and Laboratory Indexes:** There was no statistical significant correlation between TST, any specific sleep stage, arousal index, or days in the ICU with LIS or APACHE II scores. As expected, LIS and APACHE II scores were significantly correlated \((r^2 = 0.65, p = 0.003)\). There was no significant correlation between positive or negative culture results (all sources) and any stage of sleep. Nine patients had temperatures \(> 38.5^\circ\text{C}\), and five patients had temperatures \(< 36.8^\circ\text{C}\). When temperature was compared to sleep stage, again there was no correlation. It was noted that three of five patients with temperatures \(< 36.8^\circ\text{C}\) had the lowest amount of mDelta activity. Too few patients had renal insufficiency and/or hyperbilirubinemia to perform an analysis on their effect on sleep architecture. There was no association between ventilator mode and arousals \((p = 0.96)\) or awakenings \((p = 0.78)\). PS and IMV/PS mode were combined, as only two patients received PS ventilation alone. Volume control/SIMV

### Table 3—Sleep Architecture Between Groups*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Values</th>
<th>IS Group</th>
<th>CS Group</th>
<th>CS/NMBA Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, h</td>
<td>8</td>
<td>10.09 ± 6.4</td>
<td>14.1 ± 6.3</td>
<td>18.9 ± 4.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Stage I, %†</td>
<td>2–7</td>
<td>5.8 ± 6.6</td>
<td>20.8 ± 35.5</td>
<td>7.4 ± 5.9</td>
<td>0.40</td>
</tr>
<tr>
<td>Stage II, %†</td>
<td>51–72</td>
<td>57.7 ± 23.8</td>
<td>28.24 ± 35</td>
<td>48.8 ± 22.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Stage SWS-mDelta, %†</td>
<td>31.9 ± 24.6</td>
<td>49.6 ± 49</td>
<td>43.7 ± 28</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Stage SWS-Rechtschaffen and Kales, %†**</td>
<td>31.9 ± 24.6</td>
<td>48.9 ± 50.5</td>
<td>38.9 ± 28.1</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>REM sleep, %†</td>
<td>17–25</td>
<td>3.6 ± 5.7</td>
<td>NA§</td>
<td>NA§</td>
<td></td>
</tr>
<tr>
<td>Wake time, %†</td>
<td>10–15</td>
<td>54.2 ± 22.7</td>
<td>36 ± 28</td>
<td>22 ± 12.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Arousals per hour, No.∥</td>
<td>10–15</td>
<td>6.1 ± 2.4</td>
<td>5.0 ± 2.9</td>
<td>9.6 ± 10.8</td>
<td>0.80</td>
</tr>
<tr>
<td>Total arousals</td>
<td>158 ± 50</td>
<td>121 ± 69</td>
<td>230 ± 106</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Total awakenings</td>
<td>32.8 ± 10</td>
<td>58.3 ± 59</td>
<td>74.3 ± 53</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>awakenings per hour</td>
<td>4.24 ± 2.4</td>
<td>4.79 ± 3.7</td>
<td>4.4 ± 3.7</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>37.5 ± 16.7</td>
<td>71.5 ± 64†</td>
<td>150 ± 140†#</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†Expressed as mean % of TST ± SD. Normal values are for patients \(> 40\) years old.32
‡Expressed as % time spent awake during 24-h period.
§NA = not analyzed; see text for explanation.
∥Normal values from Marthur and Douglas.33
¶CS and CS/NMBA groups \((p = 0.06)\).
#Nonclassifiable data not shown.
was analyzed independently and combined with pressure control/IMV.

Sleep Architecture and Correlation of Drug Dosage: Although not statistically different than the NMBA/CS group, the CS group had the highest amount of mDelta activity (49.6% vs 43%) and also the highest amount of benzodiazepine (58 mg vs 52 mg) [Table 2, 3]. The CS group had significantly more morphine (39.8 mg vs 12.8 mg) than the CS/NMBA group. Although there was a significant difference in the amount of narcotics and benzodiazepines between the IS and CS groups and the IS and CS/NMBA groups (Table 2), there was no statistically significant correlation between drug dosage and any stage of sleep. Two of the three patients in the CS group, with > 80% mDelta, received the largest doses of lorazepam per body weight of any group.

DISCUSSION

This is the first study to our knowledge to prospectively compare various groups of critically ill patients requiring mechanical ventilation based on medication regimen. This is one of the largest studies investigating sleep in severely ill patients in the ICU and adds new information in a novel group of patients: those receiving chemical paralysis. As noted in previous studies, patients requiring mechanical ventilation, all of our patients displayed abnormal sleep/wake cycles with erratic progression through the sleep stages. No patient demonstrated normal 90- to 120-min sleep cycles with progressive increases in REM duration. Overall TST was not reduced in any group and was increased in those patients receiving CS, as anticipated. Patients were not quantitatively sleep deprived, but > 50% of sleep occurred during the daytime period, illustrating the disruption of nighttime sleep, alteration in normal circadian rhythm, and the importance of daytime sleep periods in preventing sleep deprivation. In contrast to the study of Gabor et al., in which REM sleep was determined to be normal, we found REM sleep to be severely reduced in the IS group and could not be comparatively analyzed with the other groups due to lack of detection in the patients receiving NMABs, and only 50% of patients in the CS group had detectable REM. Decreased REM sleep observed in this study may have several causes, including use of vasopressor agents, narcotics, and increased difficulty in detecting REM in patient with neuromuscular blockade.

In contrast to prior studies that reported increased stage 1 and stage 2 sleep and decreased SWS, we found increased stage 1 sleep only in the CS group, decreased stage 2 sleep only in the CS group, and increased SWS in all groups. Patients who received IS had the lowest TST but largest amount of stage 2 sleep (57.7%). Intermittent doses of benzodiazepines are known to increase spindle activity and may have contributed to the increased stage 2 sleep compared to the other groups. Environmental noise, talking, and patient-care activities have been shown to account for 30% of arousals or awakenings in ICU patients. The IS group had the least amount of patient-care interventions but the largest amount of wake time, and may have been influenced by these factors more than the other two groups receiving CS. The CS/NMBA group had the largest number of arousals and awakenings, although no correlation was established with the number of patient-care interventions and may reflect the low power of the study. Delayed arousals, > 1 min from the event, were noted with invasive procedures. Not all patients in the CS/NMBA group received narcotics, and underlying pain may have contributed to higher spontaneous and procedure-related arousals. Although sedated, their EEG reflected wakefulness 22% of the time; how this impacted their clinical outcome is unknown.

Compared to a recent study by Parthasarathy and Tobin, we did not find a relationship between awakenings or arousals and ventilator mode. In their study, 6 of 11 patients had congestive heart failure likely contributing to the central apneas associated with PS ventilation. Our patient population consisted mainly of individuals with COPD and pneumonia leading to respiratory failure. Although none of our patients were receiving assist-control ventilation, 12 patients received SIMV with mechanical ventilator rates and there was no difference in arousals or awakenings compared with the 6 patients with PS or SIMV changed to PS ventilation. Our patients may have been more critically ill and were also receiving sedation, which may have contributed to the decreased effect of ventilator mode on sleep fragmentation.

All patients demonstrated increased delta activity. Until recently, studies have excluded patients who were receiving sedation or who were critically ill. Cooper and colleagues investigated sleep patterns in 20 critically ill patients receiving mechanical ventilation who received CS and describe a large proportion of patients with increased delta activity. Patients were retrospectively categorized into three patient groups based on the following EEG features: disrupted sleep (all stages of sleep were present); atypical sleep where abnormal sleep stage transition was present (absent stage 2 sleep); or the presence of coma ( > 50% delta waves). The patients with dis-
ruptured sleep showed predominately stages 1 and 2 sleep in agreement with other studies. However, the other two groups of patients demonstrated marked increases in delta activity. They reported that 12 of their 20 patients had “unidentifiable electrophysiologic sleep.” Seven of the patients had >50% delta activity thought to be consistent with encephalopathy or coma, and five patients had atypical EEG patterns (no stage 2). Severity of illness scores, sedatives, and narcotic doses were higher among these patients, although no discernable etiology was identified to explain the increase in delta activity.

In agreement with the study by Cooper et al, we demonstrated increased delta activity in all three groups by both scoring methods. Our patients who received CS had larger amounts of delta activity than patients who received only IS. Patients in the IS group had less slowing of the delta waves and slightly higher amplitude compared to the CS and CS/NMBA groups (Fig 1, 2). Only four of our patients (three patients were in the CS group) had >50% delta activity, and all of these patients were intermittently observed to be awake or with spontaneous movement, which does not appear to support coma as the etiology. All patients in the CS and CS/NMBA groups demonstrated variability in EEG with intermittent changes in wave frequency, sustained periods of α activity, or α superimposed on the delta activity.39–45

Electrolyte imbalance, liver failure, renal failure, anoxic-ischemic brain injury, drugs, and sepsis may all contribute to encephalopathy.39–46 None of our patients had neurologic signs that may be associated with encephalopathy, such as tremor, myoclonus, or asterixis. Four patients had an elevation, albeit slight, in serum creatinine, and three of them were in the IS group and were totally alert. Only two patients had an elevation (insignificant) in serum bilirubin. No patient had oxygen saturations < 90% or systolic BP < 90 mm Hg, which could be associated with anoxic or ischemic encephalopathy. Although the groups did not differ statistically between APACHE II scores, patients in the CS and CS/NMBA groups had higher a LIS, presence of ARDS, use of vasopressor agents, and higher mortality, indicating a sicker group of patients compared to the IS group. Severity of illness may account for the change in sleep pattern but was not significant due to the small sample size. A trend was noted in increasing TST and LIS and APACHE II scores, potentially indicating greater requirements for sleep with increasing severity of illness.

Drug effect from benzodiazepines, although statistically insignificant, may have had a clinical effect. IV injection of a benzodiazepine initially causes an increase in β activity followed by a dose-dependent progressive increase in delta frequency and reduction in EEG amplitude consistent with decreased

![Figure 1](image-url)
cerebral metabolism.\textsuperscript{36,43} In patients who are critically ill, dose-dependent relationships are highly variable based on renal and hepatic metabolism as well as volume of distribution. When overdosage occurs, various EEG patterns may develop such as α-delta, burst suppression, diffuse slowing, and progression to electrocerebral silence.\textsuperscript{36,43–46} Light levels of sedation are induced at 0.1 to 0.2 mg/kg of midazolam in healthy subjects (lorazepam dose equivalent is approximately 50%). Either repeat bolus doses or continuous IV infusion at approximately 50% of the dose can maintain sedation. It is unlikely that the increased mDelta activity seen in the CS group was related to other drugs, as only one patient received additional sedation with haloperidol.

Increased low amplitude delta waves may be related to septic encephalopathy. In the study by Cooper et al.,\textsuperscript{7} septic encephalopathy was thought less likely due to negative blood culture results. However, in the study by Gabor et al.,\textsuperscript{8} five of seven patients had positive blood culture findings, but SWS was only 2.7% of TST. Many of our patients had positive culture results (all sources), but only one patient had a positive blood culture result; no correlation existed with mDelta activity. It is well supported in the literature that 50% of patients admitted to the ICU with pneumonia do not have positive culture results,\textsuperscript{47} particularly if they have received antibiotics. Therefore, systemic inflammatory response to infection despite negative blood culture results cannot be eliminated. Cytokines released, specifically interleukin (IL)-1 and tumor necrosis factor (TNF), lead to an increase in delta activity. IL-1 and TNF act in the thermoregulatory area of the hypothalamus and induce a pyogenic and somnogenic effect.\textsuperscript{48,49} Delta activity occurs in response to an increase in cerebral or body temperature. Although no correlation of temperature (fever) with mDelta was found, the majority of patients were admitted with fever, pneumonia, ARDS, and likely sepsis syndrome. We did not draw IL-1 or TNF levels, which may have been helpful in correlating delta activity. Delta activity in normal subjects is strongly related to prior wakefulness and sleep deprivation (homeostatic need for sleep).\textsuperscript{32} It is unknown how much sleep is required during illness and whether increased delta activity may be due to homeostatic need for restorative sleep. Serial EEG analysis throughout illness would be helpful to reevaluate delta amplitude and recovery.

It is well documented that SWS declines with aging.\textsuperscript{50} However, numerous studies\textsuperscript{25,26,51–53} using frequency and period amplitude analysis indicate that the amount of delta activity is actually preserved but that wave amplitude decreases significantly with age. Although it was not statistically significant, there was a 5% increase in delta activity in the CS/NMBA group using the mDelta amplitude criteria compared with standard criteria of Rechtschaffen and Kales (Table 3). This difference may reflect the effect of age in the CS/NMBA group. Scoring with traditional Rechtschaffen and Kales criteria may underestimate SWS in middle-aged and older populations. Some researchers\textsuperscript{50} have suggested that traditional amplitude criteria be abandoned and frequency scoring be implemented.

Gender is shown to have little objective effect on
polysomnography sleep architecture or sleep regulation. Women (age > 50 years) may have slightly better SWS preservation than men. Power spectral analysis has shown a small increase in delta, theta, and lower α frequencies in women compared with men. Normative data during illness will be needed to establish whether the increase in delta activity in these patients reflects cerebral dysfunction. Certainly in the IS group who were fully awake, alert, and responsive with minimal drug influence, cerebral dysfunction is less likely an etiology of increased delta activity.

Limitations

Our study had several limitations. The sample size was too small to allow for logistic regression, and several factors may confound the results. Because the study was underpowered, negative findings must be interpreted cautiously. The wide SD reflected the large variability in the groups and results could have been affected by one or two subjects. Blood drug levels were not drawn so we are unable to evaluate the actual drug level, dosage, and stages of sleep between groups. IL-1 and TNF levels also were not obtained, so a clear determination of the effect of sepsis is unknown. Although we sought to control for extraneous variables by limiting our patient population to only medical ICU patients with respiratory diagnoses, patients were not randomized and the groups differed in type of respiratory diagnosis and gender distribution. This could have led to a preselection bias based on the preexistence of the medication regimen alone. Finally, normative sleep data during illness is lacking.

Summary

This study suggests that 24-h continuous monitoring of sleep, an unrecognized vital sign, may be helpful in critically ill patients. Although patients receiving NMBA were sedated, they were shown to be awake by EEG criteria approximately 22% of the time. The functional significance of this is unknown. Circadian rhythm was disturbed, and daytime sleep periods were essential to prevent total sleep deprivation. TST increased as severity of illness increased. All patients demonstrated fragmented sleep and increased amounts of delta activity using the traditional Rechtschaffen and Kales amplitude criteria and a modified 50-μV criteria. The patients receiving NMBA demonstrated a nonstatistically significant 5% increase in delta activity using the mDelta criteria. The cause of fragmented sleep and increased delta is likely multifactorial and may be due to variation in methodology, age, drugs, metabolic effects related to illness, and the homeostatic effect on delta activity. Further studies are needed to delineate the independent contribution of these factors in a larger sample of critically ill patients. Use of a power spectral approach for analyzing sleep and sedation may be more sensitive in detecting changes in α and delta activity. Whether sleep disruption contributes to difficulty with weaning from mechanical ventilation and recovery from illness needs to be determined. Promoting sleep consolidation may facilitate this process.

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