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Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors

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Abstract

Objective—Disrupted sleep is a common and potentially modifiable risk factor for delirium in the intensive care unit (ICU). As part of a quality improvement (QI) project to promote sleep in the ICU, we examined the association of perceived sleep quality ratings and other patient and ICU risk factors with daily transition to delirium.

Design—Secondary analysis of prospective observational study.

Setting—Medical ICU (MICU) over a 201-day period.

Patients—223 patients with 1 night in the MICU in between two consecutive days of delirium assessment.

Interventions—None

Measurements—Daily perceived sleep quality ratings were measured using the Richards Campbell Sleep Questionnaire (RCSQ). Delirium was measured twice-daily using the Confusion Assessment Method for the ICU (CAM-ICU). Other covariates evaluated included: age, sex, race,

ICU admission diagnosis, nighttime mechanical ventilation status, prior day's delirium status, and daily sedation using benzodiazepines and opioids, via both bolus and continuous infusion.

Main Results—Perceived sleep quality was similar in patients who were ever versus never delirious in the ICU (median [IQR] ratings 58 [35-76] vs. 57 [33-78], respectively $p=0.71$), and perceived sleep quality was unrelated to delirium transition (adjusted OR 1.00, 95% CI 0.99-1.00). In mechanically ventilated patients, receipt of a continuous benzodiazepine and/or opioid infusion was associated with delirium transition (adjusted OR 4.02, 95% CI 2.19-7.38, $p<0.001$) and patients reporting use of pharmacological sleep aids at home were less likely to transition to delirium (adjusted OR 0.40, 95% CI 0.20-0.80, $p=0.01$).

Conclusions—We found no association between daily perceived sleep quality ratings and transition to delirium. Infusion of benzodiazepine and/or opioid medications was strongly associated with transition to delirium in the ICU in mechanically ventilated patients and is an important, modifiable risk factor for delirium in critically ill patients.

Keywords

Sleep; Intensive Care Unit; Delirium; Cognition; Sedation; Outcome Assessment

BACKGROUND

Delirium is an acute confusional state that is common in the intensive care unit (ICU) setting (1-3). Affecting up to 80% of mechanically ventilated ICU patients (4-8), delirium is associated with increased mortality (6-8), longer length of stay (4, 9), higher cost of care (10), and greater risk of subsequent cognitive impairment and institutionalization (11-14). The pathophysiology of delirium in the ICU is not well understood, although many preexisting and precipitating risk factors have been identified, including advanced age, chronic medical conditions, pre-existing neurocognitive impairment, sensory impairment, pain, dehydration, and polypharmacy (2, 3).

Disrupted sleep in the ICU has been proposed as a potential modifiable precipitating risk factor for delirium (15-21). Numerous studies have demonstrated that poor sleep is common in the ICU setting, and is characterized by frequent disruptions, fragmentation, increased arousals, and decreased restorative stages (22-28). Previously, we used an established, structured quality improvement (QI) model (29) to implement a multi-faceted sleep-promoting intervention in a medical ICU (30), resulting in a significant reduction in the incidence of delirium/coma (OR 0.46, 95% CI 0.23-0.89, $p=0.02$) and a significant increase in daily delirium/coma-free status (OR 1.64, 95% CI 1.04-2.58, $p=0.03$). The objective of this secondary analysis is to evaluate the association between critically ill patients' daily perceived sleep quality ratings and subsequent transition to delirium, and also evaluate predisposing and precipitating patient and ICU risk factors for transition to delirium, as part of a MICU sleep improvement effort.

METHODS

Project Setting and Design

In this analysis, we examine the association of perceived sleep quality and other patient and ICU risk factors for transition to delirium. This secondary data analysis was performed as a part of a multi-faceted sleep quality improvement (QI) project occurring from January to July 2010. The setting for this QI project was the Johns Hopkins Medical ICU (MICU) which, at the time of this project, had 16 private rooms and a 1:2 registered nurse (RN) to patient ratio.

All patients spending 1 night in the MICU were eligible for outcome measurement. To evaluate risk factors specifically associated with transitioning from a “normal” (i.e., non-delirious/non-comatose) state to delirious state in the ICU, this analysis was performed on a subset of patients in which delirium was assessed both before and after a full night in the MICU. Only data from patients’ first MICU admission during the project were analyzed.

Primary Outcome Variable: Transition to delirium

Twice-daily delirium and coma assessments were performed by trained MICU nurses at approximately 8am and 8pm using the reliable and valid Confusion Assessment Method for the ICU (CAM-ICU) (5) and Richmond Agitation Sedation Scale (RASS) (31), respectively. Coma was defined as a RASS score of -4 or -5 (31), as done in prior research (32-34).

Exposure Variables

All available exposure variables that could potentially predispose (i.e., demographic and home sleep characteristics) or precipitate (i.e., sleep quality and sedating medications used in the ICU) the transition to delirium were evaluated. Perceived sleep quality, the primary exposure variable, was assessed using the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ is validated 5-item questionnaire that uses a 100 mm visual-analogue scale to evaluate sleep (1) depth, (2) latency, (3) efficiency, (4) quality, and (5) number of awakenings, with higher scores representing better sleep and the average of all scores representing overall sleep quality (35). As done in prior studies (36, 37), a sixth item, evaluating perceived nighttime noise, was also included with the RCSQ, with higher scores representing less nighttime noise. Each day, all non-comatose, non-delirious patients were asked to complete the RCSQ describing the previous night’s sleep. If the patient was delirious or was unable to complete the survey due to communication barriers (i.e., non-English speaking or unable to use a writing instrument to complete the visual-analogue scale), the nightshift nurse completed the RCSQ, based on prior studies demonstrating high patient-nurse agreement on the RCSQ in non-delirious patients (36, 37).

Demographic and Clinical Variables

Demographic and ICU variables available for this analysis were: age, gender, race, ICU admission diagnosis, nightly mechanical ventilation status, and daily use of infusions and of as-needed bolus doses for both benzodiazepines and opioids. Propofol was rarely used and consequently could not be evaluated in this analysis. A baseline home sleep quality questionnaire (adapted from the Pittsburgh Sleep Quality Index (38)) querying pre-existing

sleep problems, home sleep habits, and the frequency of any sleep medication use was collected via interview with MICU patients or their proxies.

Statistical Analysis

Data were summarized using median and interquartile range for continuous variables and proportions for categorical variables. Comparison of baseline characteristics for patients who were ever- versus never-delirious in the ICU was performed using Wilcoxon rank sum for continuous variables and chi-square (or Fishers exact tests, where appropriate) for categorical variables.

The association of perceived sleep quality with transition to delirium within 24 hours was evaluated using multivariable logistic regression. Generalized estimating equations were used to account for within-patient correlations of repeated daily outcome measures. Similar to previous analyses (39), we performed this analysis using a Markov model (40), a regression model which included a patient's delirium status on the immediately prior day as a covariate. To identify covariates for the multivariable Markov model, we performed bivariable logistic regression analysis for delirium on the current day as a function of prior day delirium status and each relevant variable potentially influencing delirium, including age, gender, home sleep quality ratings, nighttime mechanical ventilation status, and four variables for as-needed bolus and infusion administration of benzodiazepines and of opioids.

To avoid over-fitting the multivariable regression model, the covariates for inclusion in the model were selected *a priori* if they had a bivariable association of $p \leq 0.20$ with the primary outcome. Multicollinearity was assessed using variance inflation factors, and addressed by recategorizing or omitting less relevant collinear variables. Specifically, in this data set, 118 of the 124 (95%) benzodiazepine infusions were given concurrently with opioid infusions; consequently, these two variables were combined into a single variable (referred to as "sedative infusion") in order to prevent multicollinearity. The possible statistical interaction between home sleep quality ratings and home sleep medication use, and nightly mechanical ventilation status and administration of sedative infusions, with the primary outcome was assessed by adding interaction terms to the multivariable model. A significant interaction was noted between ventilator status and sedative infusions and was included in the final multivariable regression model. In regression analyses, the appropriate modelling of continuous variables was confirmed via evaluating their linear association with the log odds of transition to delirium using a scatterplot with a LOWESS smoother (41). A two-sided significance level of $p < 0.05$ was used to denote statistical significance. All analyses were performed using STATA version 11.2 (College Station, TX).

An institutional review board (IRB) chair at Johns Hopkins University reviewed this MICU-wide sleep promotion effort and deemed it "quality improvement," not requiring patient consent or IRB approval.

RESULTS

During this 201-day project, 386 unique consecutive patients were admitted to the MICU. Based on the previously-described eligibility criteria for conducting this delirium transition

model, 223 (58%) patients were included, accounting for 1,129 patient-days of data collection. Among these 223 patients, 100 (45%) never developed delirium in the MICU. Of the remaining 123 (55%) patients who ever experienced delirium, 31 (25%) ever transitioned from normal cognition (i.e., a non-coma and non-delirious state) to delirium a total of 47 times: 23 transitioned once, 5 transitioned twice, and 1 patient each transitioned three, five, and six times.

Between those who never versus ever experienced delirium in the ICU, there were no significant differences in sex, race, or admission diagnosis (Table 1). However, ever- versus never-delirious patients were significantly older (median [IQR] age 59 [45-70] versus 53 [45-61], $p=0.02$), more likely to receive mechanical ventilation in the ICU (73% versus 33%, $p<0.001$), and less likely to have a history of sleep problems (18% versus 34%, $p=0.008$) and use pharmacologic sleep aids at home (11% versus 27%, $p=0.003$).

Regarding sedation medications, compared to never-delirious patients, significantly more ever-delirious patients received benzodiazepine boluses (34 of 123 [28%] versus 11 of 100 [11%], $p=0.002$), opioid boluses (53 [43%] versus 28 [28%], $p=0.03$), and opioid and/or benzodiazepine infusions (51 [41%] versus 15 [15%], $p<0.001$). Among the 123 mechanically ventilated patients, 39 (32%) received bolus benzodiazepines, 55 (45%) received opioid boluses, and 56 (46%) received a benzodiazepine and/or opioid sedative infusion during the course of their ICU stay.

Sleep Quality and Noise Ratings

Comparing ever- versus never-delirious patients, there was no significant difference in daily ratings of perceived overall sleep quality (median [IQR] 58 [35-76] versus 57 [33-78], $p = 0.71171$) or noise (69 [50-81] versus 65 [46-85], $p = 0.33$), and no significant differences in any of the five individual RCSQ sleep quality item ratings.

Factors related to delirium transition

In bivariable logistic regression models, there was no significant association between demographic variables or nightly overall sleep quality ratings with transition to delirium (Table 2). Receiving mechanical ventilation and any sedative infusion (i.e., opioid and/or benzodiazepine) was associated with delirium transition; however, bolus administration of either opioids or benzodiazepines was not. In a multivariable logistic regression model, we adjusted for age; race; self-reported sleep quality and use of sleep aids at home; daily perceived sleep quality ratings; nightly mechanical ventilation status; sedation infusion; and a statistical interaction term for the latter two variables, as previously described in the Statistical Methods (Table 2). This regression model demonstrated a significant synergistic association between mechanical ventilation status and sedation infusion for transition to delirium (OR 4.02, 95% CI 2.19-7.38, $p<0.001$ for receiving sedation infusion with mechanical ventilation). In addition, self-reported use of home pharmacological sleep aids had a significant inverse association with transition to delirium (OR 0.40, 95% CI 0.20-0.80, $p=0.01$). Finally, the results were not materially changed when performing post-hoc sensitivity analyses that adjusted for RCSQ rater (patient versus nurse) or the presence of

interventions performed as part of the sleep QI project, or when restricting the analysis to include only patients' first delirium transitions.

DISCUSSION

As part of a prospective, multi-faceted quality improvement (QI) project to promote sleep in a medical ICU (MICU), this secondary analysis was undertaken to determine whether daily perceived sleep quality ratings were associated with subsequent transition to delirium in the ICU. Our analysis of 223 critically ill patients demonstrated no association of daily perceived sleep quality ratings and transition to delirium. However, for patients receiving mechanical ventilation, receipt of a sedative (i.e., benzodiazepine and/or opioid) infusion was strongly associated with transition, in the next 24 hours, from a non-delirious to delirious state.

Despite decades of interest in the association between sleep deprivation and delirium, few ICU-related studies have been published in this specific area. Early case reports of healthy individuals described psychotic features, memory lapses, and labile mood when undergoing prolonged wakefulness (43). Observations in ICU populations have reported mental status changes in 62 critically ill medical-surgical patients with a high number of observed sleep interruptions (16), and post-operative delirium in a subset of 432 thoracic surgery patients reporting subjective sleep deprivation (44). Moreover, polysomnography in 29 mechanically ventilated patients demonstrated that delirium, as measured with the CAM-ICU, was more frequent when there were severe reductions in rapid-eye movement (REM) sleep (45).

Our sleep QI project, the source for this secondary data analysis, was conducted in an effort to understand the role of sleep promotion on ICU delirium and patient outcomes after ICU discharge (46). In this pre-post project, we implemented a MICU-wide, multi-faceted sleep promoting intervention and observed a significant reduction in the incidence of delirium/coma during the ICU stay and a significant increase in daily ICU delirium/coma-free status (30). Our current secondary analysis aimed to build upon these findings by evaluating the specific association, if any, between modifiable ICU factors such as sleep quality and sedating medications and development of delirium. In performing prospective daily assessments of sleep quality and delirium, using validated measurement tools, for all patients in our MICU, we expanded on prior studies which were limited in sample size (16, 45), used non-validated tools to assess sleep quality (16, 44), and/or did not measure sleep and/or delirium on a daily basis (16, 44, 45).

Our findings suggest that perceived sleep quality was not associated with transition to delirium. This finding must be considered within the context of two important issues related to our study design. First, we measured sleep using the RCSQ since it was validated previously (35) against polysomnography (PSG), the gold standard for sleep measurement, and was feasible to collect daily for all patients in the ICU. Second, when patients were delirious or unable to complete the RCSQ (e.g., language barrier, or inability to use a writing instrument), their nurse completed the RCSQ on their behalf, based on prior literature suggesting high patient-nurse agreement on the RCSQ (36, 37). However, a separate sub-analysis of patient-nurse agreement, performed as part of our sleep QI project, demonstrated

that nurses tended to overestimate patient sleep quality on the RCSQ (47) which would bias our analysis towards the null hypothesis of no association between perceived sleep quality and delirium. Further evaluation of transition to delirium and ICU sleep quality, evaluated using PSG, is required to address these limitations of our research.

A notable finding of this analysis was the strong, independent positive association of sedative infusions with delirium transition in mechanically ventilated patients. This finding underscores the importance and generalizability of recent publications (48-51), clinical practice guidelines (21) and “Choosing Wisely” recommendations (52) promoting efforts to minimize sedative exposure in critically ill patients. Given the infrequent use of benzodiazepine-only infusions during our study (i.e., almost always co-administered with an opioid infusion), we are unable to tease apart any differential effect of infusion of each of these types of medications. However, based on recent clinical practice guidelines (21), analgesia should be provided prior to the use of benzodiazepines to help ensure appropriate pain control and minimize delirium risk.

A second notable finding in our analysis is the negative association between self-reported home use of pharmacologic sleep aids and delirium transition. This finding suggests that there may be an attenuated response to sedative medications in these patients, presenting an interesting area for further investigation.

In addition to these areas of discussion, there are other potential limitations of this analysis. First, because the sample size of eligible patients (i.e., spending 1 night in MICU and having 1 night of sleep assessment) was relatively small, our analysis may have been underpowered to identify all significant risk factors for transition to delirium. However, this analysis demonstrated important findings regarding sedation infusions in mechanically ventilated patients and is a foundation for larger future studies. Second, in this secondary analysis, we did not have access to data on attempted interventions to mitigate delirium, such as reorientation, administration of antipsychotic medications, discontinuation of deliriogenic medications, and treatment of physiological abnormalities, or on other potentially relevant risk factors for delirium, such as illness severity, use of physical restraints, and use of other deliriogenic medications (e.g., anticholinergics and corticosteroids (51)). Additionally, our data collection of sedative medications did not include daily drug dosage, which may have limited power to evaluate a potential dose-response effect of bolus administration of benzodiazepines and opioids on delirium transition. Third, as previously described, we used the validated RCSQ instrument instead of PSG, which is challenging to perform in the ICU on a large-scale basis (53, 54). Fourth, generalizability of our findings may be limited, given that our analysis was performed in a single MICU. However, our analysis was conducted as part of routine care and included all patients admitted to the MICU without any exclusion criteria. Moreover the results were consistent with prior literature in other ICU populations. Together, these factors help support the generalizability of the results.

In conclusion, in this analysis performed as part of an ICU-wide, multi-faceted QI project to promote sleep in a MICU, our results did not demonstrate an association between nightly perceived sleep quality ratings and subsequent transition to delirium. However, the infusion

of sedative (i.e., benzodiazepine and/or opioid) medications in the setting of mechanical ventilation was strongly associated with delirium transition, supporting recent recommendations to minimize sedation in the ICU. Further evaluation, using validated measures of both sleep and delirium, is required to further clarify the role of sleep on delirium in the ICU.

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Table 1Baseline demographic features, stratified by delirium status (ever or never) over entire ICU admission^a

Characteristic or exposure	All Patients (N=223)	Never Delirious (N= 100)	Ever Delirious (N = 123)	P value ^b
Demographic variables				
Age, median (IQR), y	55 (45 - 66)	53 (45 - 61)	59 (45 - 70)	0.02
Male, n (%)	114 (51)	49 (49)	65 (53)	0.59
Race, n (%)				0.12
White	105 (47)	47 (47)	58 (47)	
Black	106 (48)	51 (51)	55 (45)	
Other	12 (5)	2 (2)	10 (8)	
Home sleep variables				
Self-reported history of sleep problems, n (%)	56 (25)	34 (34)	22 (18)	0.008
Watches TV while sleeping, n (%)	81 (36)	36 (36)	45 (37)	1.00
Uses pharmacologic sleep aids, n (%)	40 (18)	27 (27)	13 (11)	0.003
Self-reported home sleep quality, n (%)				0.16
Very good	62 (28)	25 (25)	37 (30)	
Somewhat good	72 (32)	39 (39)	33 (27)	
Bad	45 (20)	21 (21)	24 (20)	
Unknown / Not answered	44 (20)	15 (15)	29 (24)	
ICU variables				
Admission diagnosis category, n (%)				0.07
Respiratory Failure	80 (36)	34 (34)	46 (37)	
Gastrointestinal	34 (15)	14 (14)	20 (16)	
Sepsis	27 (12)	7 (7)	20 (16)	
Cardiovascular	25 (11)	16 (16)	9 (7)	
Other	57 (26)	29 (29)	28 (23)	
Ever received mechanical ventilation, n (%)	123 (55)	33 (33)	90 (73)	<0.001
Ever received benzodiazepine bolus, n (%)	45 (20)	11 (11)	34 (28)	0.002
Ever received opioid bolus, n (%)	81 (36)	28 (28)	53 (43)	0.03
Ever received infusion (opioids or benzodiazepines), n (%)	66 (30)	15 (15)	51 (41)	<0.001

IQR = interquartile range. Percentages rounded to nearest integer.

^aSubset of MICU patients who spent ≥ 1 night in the MICU and who had at least 1 subsequent delirium assessment after a full night in the MICU.^bCalculated using Wilcoxon rank sum for continuous variables, and chi-squared or Fisher's exact tests, as appropriate, for categorical variables.

Table 2

Demographic, ICU, sedation and sleep measures and daily transition to delirium

Covariate	Bivariable OR (95% CI)	P value ^a	Multivariable OR (95% CI)	P value ^b
Demographic variables				
Age, per year	1.01 (1.00, 1.02)	0.20	1.01 (1.00, 1.02)	0.07
Male	0.99 (0.67, 1.46)	0.96		
Race		0.18		0.19
White	REF		REF	
Black	0.84 (0.55, 1.28)		0.76 (0.49, 1.17)	
Other	1.60 (0.82, 3.10)		1.63 (0.65, 4.12)	
Home sleep variables				
Self-reported history of sleep problems	0.85 (0.49, 1.46)	0.56		
Watches TV while sleeping at home	0.95 (0.64, 1.42)	0.80		
Uses pharmacological sleep aids at home	0.39 (0.19, 0.77)	0.007	0.40 (0.20, 0.80)	0.01
Self-reported home sleep quality		0.15		0.24
Very good	REF		REF	
Somewhat good	0.86 (0.54, 1.37)		1.01 (0.59, 1.73)	
Somewhat/very bad	1.20 (0.69, 2.08)		1.31 (0.72, 2.38)	
Unknown / not answered	1.86 (0.97, 3.56)		1.91 (0.94, 3.87)	
ICU variables				
ICU admission diagnosis		0.68		
Respiratory (including pneumonia)	REF			
Gastrointestinal	0.82 (0.46, 1.48)			
Sepsis (non-pulmonary)	1.36 (0.75, 2.49)			
Cardiovascular	0.79 (0.33, 1.90)			
Other	0.93 (0.55, 1.57)			
Total quality on RCSQ, per point ^c	1.00 (0.99, 1.01)	0.86	1.00 (0.99, 1.00)	0.45
Receiving mechanical ventilation overnight	2.09 (1.41, 3.11)	<0.001		
Receiving mechanical ventilation without sedation ^d			1.27 (0.85, 1.91)	0.25
Received bolus opioids	0.83 (0.55, 1.23)	0.35		
Received bolus benzodiazepines	0.96 (0.57, 1.60)	0.87		
Received sedative infusion (benzodiazepine or opioid)	2.42 (1.49, 3.96)	<0.001		
Received sedative infusion while not mechanically ventilated ^d			0.45 (0.17, 1.16)	0.10
Received sedative infusion while mechanically ventilated ^d			4.02 (2.19, 7.38)	<0.001

OR, Odds Ratio; CI, Confidence Interval; RCSQ, Richards-Campbell Sleep Questionnaire

^a Calculated using bivariable logistic regression^b Calculated using multivariable logistic regression analysis using generalized estimating equations to account for within-patient clustering of repeated daily delirium assessments. Variables included in this model were the primary outcome variable (daily perceived sleep quality) and other covariates that had a bivariable association of $p \leq 0.20$ with the primary outcome.^c Higher scores represented better sleep quality for the overall sleep rating, and less overnight noise for the noise component.

^d Assessed using interaction term in the multivariable regression model.