Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit*

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Objective: **Describe the pharmacoepidemiology of sedative medications and nurse-rated patients' behavior and sedation adequacy.**

Design: **Cohort study, 2001–2003.**

Patients: **Patients ventilated for >36 hrs in a medical or surgical intensive care unit at a university-affiliated hospital. Proxies for 312 eligible subjects were approached for consent, 277 subjects enrolled, and data from 274 subjects were analyzed.**

Interventions: **None.**

Measurements and Main Results: **Distribution of Arousal and Motor Activity levels, proportion of inadequate sedation and factors associated with inadequate sedation, variation of sedative therapy intensity, and behavior over time were measured. Sedatives were administered in 85% of 18,050 four-hour intervals during mechanical ventilation. Sedation was judged as adequate in 83% of 12,414 sedation assessments; patients were judged to be undersedated in 13.9% and oversedated in 2.6% of the assessments. Patients were unarousable or minimally arousable 32% of the time and had no spontaneous motor activity (during a 10-min observation period) 21.5% of the time. There was little variation in level of consciousness or motor activity or drug dose over 24 hrs, but daytime caregivers were more likely to judge patients as oversedated (3.7%) compared with nighttime caregivers (1.6%, $p < .001$). Inadequate sedation was associated with sedative drug intensity and patient behavior as measured by a two-domain sedation scale. Sedative drug intensity and behavior varied during the course of respiratory failure, and survivors received 13% more sedation per 4-hr interval of mechanical ventilation than nonsurvivors ($p < .001$).**

Conclusions: **Although patients were minimally arousable or nonarousable in 32% and motionless in 21% of the sedation assessments, surprisingly, an oversedation rating occurred in <3%. This discrepancy, along with findings that time of day influences the interpretation of sedation adequacy and that patients' behavior change over time suggests that collaborative research is needed to define adequate sedation. (Crit Care Med 2007; 35:393–401)**

KEY WORDS: sedation; intensive care units; critical illness; acute respiratory failure

Most patients requiring mechanical ventilation are treated with sedative medications such as opiates, benzodiazepines, and propofol (1–5). These medications are given for a wide range of indications (6, 7) best summarized as reducing the physiologic and psychological stress of respiratory failure and improving the tolerance of invasive life support.

Investigations have demonstrated the benefits of using sedation rating scales and protocols that minimize sedative exposure (8–12). Other types of studies have included comparative drug trials (13), sedation scale validation studies (14), and surveys on sedation practice (1, 2, 4). However, previous work has not addressed questions such as: Which characteristics are associated with caregivers' judgment of inadequate sedation, and how often does inadequate sedation occur in practice? How does sedative therapy and patient behavior change throughout the day and during the course of an episode of respiratory failure? Exploring these questions is important for two reasons. First, achieving a high rate of global sedation adequacy may serve as a quality of care indicator. Second, adoption of sedation protocols might increase if medical and nursing caregivers (and possibly patients' families) share common ground on what constitutes "adequate sedation" over time.

Therefore, our objective was to measure, in fine detail and over an entire episode of respiratory failure, the epidemiology of sedative use and patient behavior and to define the factors that influence nurses' estimates of sedation adequacy.

METHODS

We conducted a cohort study of patients acutely mechanically ventilated via an endotracheal tube for ≥36 hrs in the adult medical and surgical intensive care units (ICUs) at the University of Minnesota Medical Center, Fairview. The study included a follow-up for survivors, but here we present data for all subjects collected during ICU care within the first 2 months after enrollment. Informed consent was obtained from proxies, and the study was approved by the University Institutional Review Board.

ICU Characteristics. The hospital is a transplantation and oncology center that does not accept major trauma cases. With the exception of cardiovascular and neurosurgical patients, the units (34 staffed beds) have a "closed" format, with medical and general surgical care (including sedative medication orders) delivered by resident housestaff and fel-

***See also p. 635.**

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lows led by faculty intensivists. Full-time ICU pharmacists and bedside nurses participate in daily rounds.

During the study interval (2001–2003), the ICUs had written sedation and analgesia practice guidelines (15), but there was no sedation protocol that titrated drugs to a specific level of sedation, mandated a daily dose reduction for all sedatives, or limited the use of continuous infusions.

Measurements. Approximately 3 months before study commencement and separate from this research, bedside nurses were trained to complete every 4 hrs a brief sedation assessment instrument, the Minnesota Sedation Assessment Tool (MSAT), on all intubated patients receiving sedative medications. The MSAT (Appendix 1) was developed at the University of Minnesota Medical Center and has high interrater reliability when used by clinical nurses after minimal training (16).

Nurses recorded the maximum level of *un*stimulated motor activity observed in the 10 mins before the specified time (e.g., 12:00). Arousal level was measured by the amount of stimulation required to have the patient open his or her eyes, and then nurses would choose one of three sedation adequacy categories (undersedated, oversedated, or adequately sedated) that represent the quality of sedation in the previous 4 hrs. The MSAT differs from several published sedation scales (17–20) as it has objective measures (Motor Activity and Arousal levels) and a subjective judgment of global sedation adequacy.

Data were abstracted and analyzed by 4-hr time blocks (00:00, 04:00, 08:00, 12:00, 16:00, and 20:00 hrs). 08:00, for instance, represents the MSAT performed at 8 am and the sedatives given during the previous 4 hrs. We defined eight medications as "sedatives" (6, 13). Summed doses of midazolam, lorazepam, fentanyl, morphine, hydromorphone, and haloperidol dosages (in milligrams) given during a 4-hr time block were converted to milligrams per kilogram per hour based on the ICU admission weight. We recorded whether these medications were administered as a continuous infusion during each interval. A 10-mg dose of intravenous morphine was defined as equivalent to 1.5 mg of hydromorphone and 0.1 mg of fentanyl (21); 3 mg of midazolam was defined as equivalent to 1 mg of lorazepam (22). Propofol or dexmedetomidine doses were converted to micrograms per kilogram per minute or micrograms per kilogram per hour, respectively. We analyzed 18,050 four-hour time blocks during which a subject was intubated. Patients received a sedative medication in 15,343 of the intervals (85%) and an MSAT was documented in 12,414 (68.8%). Compliance for MSAT completion varied by <10% across the six time points.

Sedatives have different potencies and conversion methods across drug classes are not available. We created a sedative drug intensity score composed of the weight-adjusted dose of each medication administered during that time block categorized as 1 through 4 based on that drug's quartile rank across all time blocks. For instance, if 0.1 mg/kg lorazepam and 0.2 mg/kg morphine were given during a 4-hr interval and 0.1 mg/kg lorazepam was in the second quartile of all lorazepam doses in the entire cohort and 0.2 mg/kg morphine was in the third quartile, then the sedative drug intensity score for the time block was 5.

For the analysis defining sedation intensity during an episode of respiratory failure, we only analyzed cases with contiguous ventilator episodes of 3–21 days. To visually compare cases with different intubation intervals (5), days of ventilation were divided into deciles. Therefore, the fifth decile represents the midpoint of the intubation interval for all cases, although that half-way point may represent 1.5 to 10.5 days. Severity of illness was measured using a Multiple Organ Dysfunction Score (23), using the worst value for five organ systems obtained during ICU care within 2 months after enrollment. The Multiple Organ Dysfunction Score neurologic subscale was not included because it assigns a normal Glasgow Coma Scale value of 15 for "sedated" patients, whereas nurses in the University of Minnesota Medical Center ICU record the Glasgow Coma Scale based on the actual state of the patient.

Enrollment. Between August 2001 and February 2003, 954 patients required mechanical ventilation and 538 were ventilated for >36 hrs. Of these patients, 162 had exclusion criteria (craniotomy, coma of >24 hrs in the absence of sedatives, plans for ending life support, pre-ICU psychotic diagnosis, ventilated for >3 days at another hospital, residence of >150 miles from Minneapolis, or chronic cognitive or communication dysfunction precluding an in-person interview). A total of 312 proxies (83% of eligible subjects) participated in a consent discussion, and 277 subjects (89% yield) were enrolled. For this report, we excluded three subjects. One never received any sedatives and two had data abstraction errors that precluded analysis.

Statistics. Group mean values were tested for differences by Student's *t*-tests or analysis of variance or nonparametric tests, depending on the distribution. If global F tests were significant ($\alpha < 0.05$), *post hoc* comparisons were tested with the Tukey honest significant different statistic. For some analyses, weight-adjusted sedative doses were Z-transformed to a standard normal distribution. Differences in proportions were tested with chi-square analysis, with 95% confidence intervals calculated by the binomial method. We used the generalized estimating equations procedure to define factors associated with undersedation or oversedation (24). This procedure provides consistent estimators of the regression coefficients and their standard errors by accounting for the within-person correlation (we used an autoregressive covariance structure) of repeated sedation assessments on the same patient. Analyses were performed using SPSS version 11 (SPSS, Chicago, IL) or SAS (SAS Institute, Cary, NC).

RESULTS

Subjects had a broad range of indications for mechanical ventilation (Table 1). The severity of illness was high, with a median mechanical ventilation duration of 6.8 days and a median modified Multiple Organ Dysfunction Score of 7.8 (interquartile range: 5, 11). A total of 66 of 274 subjects (24.1%) died in the ICU: 52 died in their initial ICU stay, and the remainder died in subsequent ICU stays within 2 months after enrollment. Two thirds had a grossly normal level of consciousness before intubation. During the 2 months after enrollment, 19% had two episodes of mechanical ventilation and 11% had three or more episodes.

Sedative Pharmacoepidemiology. Propofol was used in 34.7% of the 18,050 four-hour time blocks, and morphine and lorazepam were used in 33.3% and 24%, respectively. Less common were hydromorphone (14.8%), fentanyl (9.1%), midazolam (8.4%), haloperidol (3.6%), and dexmedetomidine (2.6%). An opiate was administered in 56.3% of all time blocks in which a sedative was given; the median dose was 0.023 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ morphine equivalents (interquartile range: 0.009, 0.070). Opiates were administered as a continuous infusion 36.9% of the time. The median dose during continuous infusion was 0.036 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ morphine equivalents and 0.014 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ when administered as a bolus, a 2.5-fold increase ($p < .001$). A benzodiazepine was used in 31.4% of all time blocks in which a sedative was given. The median dose was 0.008 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ lorazepam equivalents (interquartile range: 0.004, 0.021), and they were administered as a continuous infusion 37.9% of the time. The median dose during continuous infusion was 0.027 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ lorazepam equivalents and 0.005 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ when administered as a bolus, a 5.4-fold increase ($p < .001$). The median propofol infusion rate (during a time block in which propofol was used) was 25 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ (interquartile range: 15, 39).

A single sedative was used in 46.8% of the time blocks during mechanical ventilation, two sedatives in 31.4%, three sedatives in 6.2%, and no sedative was administered in 15%. The most common drug combinations were propofol and an opiate or benzodiazepine and an opiate.

Table 1. Characteristics of study subjects (n = 274)

Age in years, median (IQR)	55 (47–65)
Male sex	51%
Treated in the surgical/ cardiovascular ICU	56%
Primary reason for mechanical ventilation	
Postoperative respiratory failure	35%
Pneumonia, aspiration, or acute lung injury	23%
Heart failure, pulmonary edema, or coronary ischemia	13%
Sepsis/shock	10%
Other[a]	20%
Mental status before intubation[b]	
Alert and attentive	65%
Inattentive or confused	19%
Unresponsive or unable to verbally communicate	8%
Duration[c] of respiratory failure,[d] days	
Mean ± SD	13.2 ± 17
Median	6.8
IQR	3.6–16.6

IQR, interquartile range; ICU, intensive care unit.

[a]Includes acute exacerbation of chronic respiratory disease, decreased level of consciousness, neuromuscular disease, and cardiopulmonary arrest of unclear cause; [b]we reviewed subjects' charts for documentation of mental status. Elective surgical cases were assumed to be alert and attentive before surgery unless there was documentation otherwise; 5% of charts were not available for review, and 4% could not be classified after review; [c]days on ventilator while in the University of Minnesota Medical Center ICU. Discontinuous episodes were summed for up to 2 months after enrollment. Days were not counted after ventilated patients were discharged to another facility; [d]we defined severe respiratory failure as a day of mechanical ventilation with a positive end-expiratory pressure of ≥6 cm H_2O (usually indicating a need to improve oxygenation in diffuse parenchymal disease) or an F_{IO_2} of >50% (excluding the initial few hours after intubation, at which time patients may be placed empirically on 100% oxygen). By this definition, 27% of the subjects had nonsevere respiratory failure (never had positive end-expiratory pressure of ≥6 cm H_2O or F_{IO_2} of >50%) and 73% had severe respiratory failure (38% had one or the other condition, and 36% had both).

A total of 42 subjects (15.4%) received at least one dose of a nondepolarizing muscle relaxant. Eighteen received less than or equal to two separate doses, usually for a procedure or immediately after intubation. Six subjects had continuous infusions for ≤24 hrs, and 18 subjects had continuous infusions for >24 hrs. Total hours of paralytic use were 1,823, or 2.5% of the 18,050 intervals during mechanical ventilation.

State of Intubated Patients. Figure 1 shows the distribution of patients' Motor Activity (scale of 1–4) and Arousal levels (scale of 1–6). Approximately one third of the time, subjects were unarousable or minimally arousable to moderate tactile stimuli (Arousal 1 or 2); slightly less than one third of the time, patients had their eyes open and were tracking objects in the room (Arousal 6); and slightly more than one third of the time, subjects were between the two extremes. Patients showed no spontaneous muscle movement during 21.5% of the 10-min observation periods (Motor 1). The distribution of Arousal and Motor Activity levels varied minimally throughout a 24-hr cycle. Arousal level 6 (eyes open and tracking) had the greatest variation: the proportion of ratings at Arousal level 6 decreased from 32.7% at noon to a nadir of 24.8% at 4 am. Variation across a 24-hr cycle for the other scale levels was only 3–4% (i.e., the normal diurnal pattern of daytime alertness and spontaneous movement was abolished).

For lorazepam, midazolam, morphine, and fentanyl, there were no statistically significant differences in the mean dose during the six time intervals. Mean hydromorphone doses were statistically different ($F = 3.6$, $df = 5$, $p = .003$) but without a discernible day–night pattern. Propofol ($F = 4.4$, $df = 5$, $p < .001$) doses were highest at 4 am, declined throughout the day, and then increased between 8 pm and midnight. The mean 4 am dose was statistically different from the noon, 4 pm, and 8 pm doses, but the maximum difference (between 4 am and 4 pm) was only 0.15 SD. Despite these nominal diurnal changes in both patient behavior and sedative drug intensity, nurses during the day (8 am, noon, 4 pm) were more than twice as likely to judge their patients as oversedated compared with nighttime hours: 3.7% vs. 1.6% at night (chi-square = 55.5, $p < .001$). There was no difference in the rate of undersedation by day and night: 14.3% vs. 13.6%.

Including the entire cohort, patients were judged by their nurses as undersedated in 1,731 time blocks (13.9%), oversedated in 326 (2.6%), and adequately sedated in 10,357 (83%). A total of 111 subjects (40%) received one or more ratings of oversedation, and 211 (76.2%) received one or more ratings of undersedation. Figure 2 shows that the relationship between Arousal levels and the probability of being judged as oversedated was nonlinear. Decreasing wakefulness increased the probability of oversedation only slightly until the lowest level (no movement after moderate tactile stimulation), at which the probability increased four-fold. A similar abrupt increase was demonstrated in the Motor Activity scale (Fig. 3). The relationship between Arousal and undersedation was different (resembling a step function), whereas an increase in Motor Activity level increased the probability of undersedation in a monotonic fashion.

Effects of Sedatives on Sedation Level and Quality. Figure 4 shows an inverse linear relationship between both the Arousal and Motor Activity scale and the sedative drug intensity score. The method of administration affected sedation adequacy in univariate analysis: opiates and benzodiazepines used as a continuous infusion increased the risk of oversedation compared with bolus dosing, although the absolute risk was low (Table 2). Continuous infusions also markedly decreased the risk of being rated as undersedated. Propofol (always given as a continuous infusion) showed similar differences in risk.

Factors Associated with Nonadequate Sedation. Multivariate models (Tables 3 and 4) show that both behavioral measures (Motor Activity and Arousal) were independently associated with sedation quality: higher values (more spontaneous muscle activity and more alertness) increased the odds of undersedation by 2 and 1.4 times for each increase in scale level. The relationship was similar, albeit in the opposite direction, for oversedation. In both models, sedative drug intensity was independently associated with sedation quality. In the oversedation model, time of day was associated with sedation quality; an MSAT assessment was 2.4 times more likely to be rated as oversedated during the day compared with during the nighttime, even after adjustment for patient behavior and drug dose. In ranking the relative importance of predictors of inadequate sedation, based on a stepwise approach to model building, Motor Activity had the strongest relationship in both the undersedation and oversedation models.

Sedation Intensity and Behavior During an Episode of Respiratory Failure. Figure 5 shows that the amount of sedative medication given to patients varied over the intubation interval and was related to patients' vital status at extubation. Both survivors and nonsurvivors initially received the same amount of sedatives. However, those alive at extubation had an early increase in the amount of

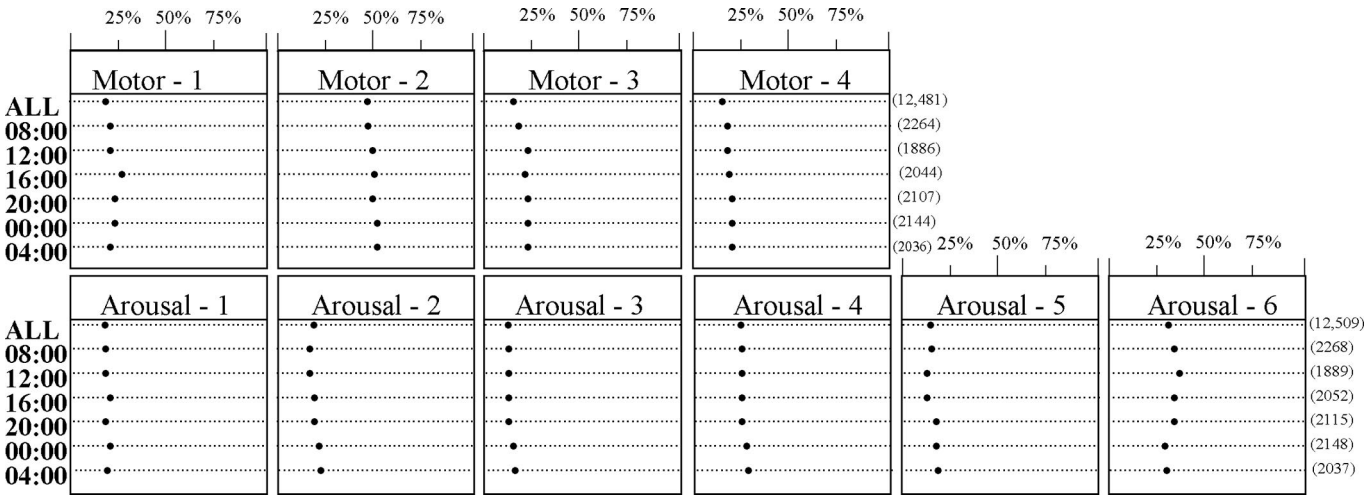

Figure 1. Multiway dot plot of the distribution of the four levels of the Motor Activity scale and the six levels of the Arousal scale. The *dot on the top line* (ALL) within each box represents the proportion of all sedation assessments at the specified Motor or Arousal level. The *six dots below* (within the same box) are the same proportions but grouped by each of the six time intervals (displayed in military time format), starting at eight o'clock in the morning. *Numbers in parentheses at the far right side* are the total counts (denominator) used to calculate the proportions. Daytime was defined as 8:00, 12:00 and 16:00 and nighttime as 20:00, 00:00, and 4:00.

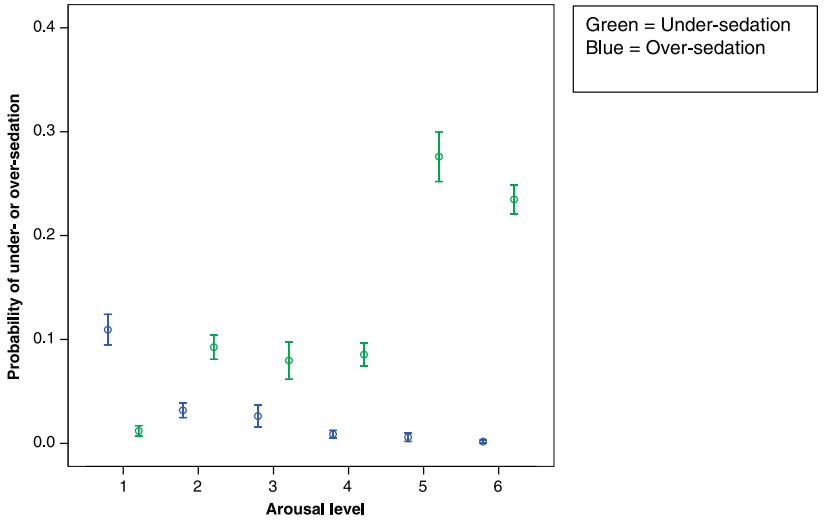

Figure 2. Relationship between Arousal Minnesota Sedation Assessment Tool (*MSAT*) score and proportion of inadequate sedation. The *y-axis* is the proportion of MSAT assessments rated as oversedated, corresponding to data series in *blue*, or undersedated, corresponding to data series in *green*. *Point estimates* are proportions; *bars* represent 95% confidence intervals calculated by the binomial method.

sedative medications that peaked in the fourth decile and then declined, with a sharp decrease in the last tenth. Sedation intensity of nonsurvivors was more variable, until the end, when there was a marked increase in sedative exposure. The mean sedative drug intensity score per time interval was 13% higher in survivors compared with patients who died ($p < .001$).

The observable behavior of patients during an episode of respiratory failure was somewhat different than the dose intensity (Fig. 6). Despite the initial increase in sedative intensity, survivors' level of consciousness increased slightly to the midway point, followed by a distinct increase in alertness coincident with the decrease in drug delivery. Spontaneous motor activity began a similar upward trend after the midpoint but with a flatter slope. For nonsurvivors, the mean Arousal level was comparable with survivors through the first two thirds of the intubation interval, even as nonsurvivors received less sedation. Nonsurvivors subsequently experienced a sharp decline in Arousal level in the last third of the intubation interval, coincident with an increase in drug administration.

DISCUSSION

Sedation therapy is a paradigm of the multidisciplinary nature of critical care that demands collaboration among nursing, medical, and pharmacy professionals. However, even with studies that show that using sedation protocols leads to improved patient outcomes, defining adequate sedation is difficult. For instance, in 19 sedation trials using the 6-point Ramsay scale, the target sedation level was defined variously as 3, 5, 2–3, 2–4, 2–5, 3–4, or 4–5. Even so, during closely monitored clinical trials, patients were at the sedation target, on average, only 69% of the time (13). Physicians surveyed about the desired level of sedation for a hypothetical patient requiring F_{IO_2} of >0.50 gave responses that ranged from 2 to 5 on the 6-point Ramsay scale (25). More recent protocols have promoted a goal of a more responsive yet comfortable patient (8, 10, 12), although a trial published in 2006 with a stated Ramsay goal of 2–3 was able to achieve that in only about 49% of the assessments (26).

Patients were judged as undersedated five times more often than oversedated. The low prevalence of an oversedated rating in a population in which patients were minimally responsive one third of the time seems to contradict sedation studies that, in various ways, promote increased patient responsiveness. Factors associated with nonadequate sedation were related to the observable behavior of the patient, time of day, amount of sedation given in the previous 4 hrs, and

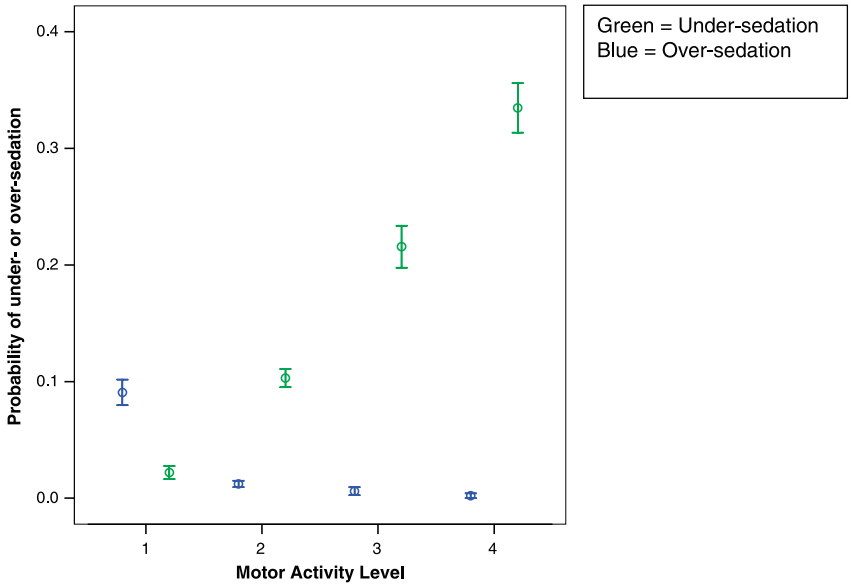

Figure 3. Relationship between Motor Activity Minnesota Sedation Assessment Tool (*MSAT*) score and proportion of nonadequate sedation. The *y-axis* is the proportion of MSAT assessments rated as oversedated, corresponding to data series in *blue*, or undersedated, corresponding to data series in *green*. *Point estimates* are proportions; *bars* represent 95% confidence intervals calculated by the binomial method.

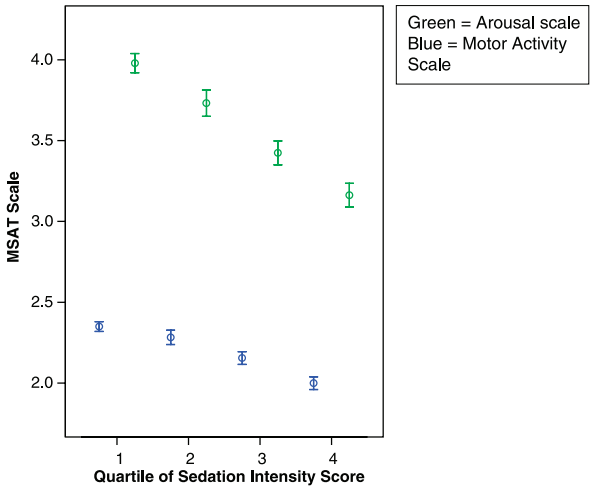

Figure 4. Relationship between quartiles of Sedation Intensity Score and Minnesota Sedation Assessment Tool (*MSAT*) domains. Displayed are Arousal (*green data series*) or Motor Activity (*blue data series*) scores for subjects within each sedative drug intensity score quartile group. *Point estimates* are mean values; *bars* represent 95% confidence intervals.

Table 2. Absolute and relative risk (RR) of inadequate sedation by method of administration or use of propofol

	Risk of Oversedation	Risk of Undersedation	RR of Oversedation (95% CI)	RR of Undersedation (95% CI)
Benzodiazepine (continuous)	0.032	0.082	1.32 (0.89–1.94)	0.37 (0.31–0.44)
Benzodiazepine (bolus)	0.024	0.219		
Opiate (continuous)	0.031	0.115	1.92 (1.38–2.67)	0.69 (0.61–0.78)
Opiate (bolus)	0.016	0.167		
Use of propofol	0.030	0.121	1.31 (1.03–1.67)	0.75 (0.67–0.82)

CI, confidence interval. Relative risk, risk of oversedation during continuous therapy divided by risk during bolus therapy (same for under-sedation and use of propofol vs. use of a sedative other than propofol).

increasing age in the case of undersedation. During daytime hours, patients were more likely to be judged as oversedated, even though there were minimal differences in the actual amount of sedatives administered and after controlling for Motor Activity and Arousal levels. In fact, performing a sedation assessment during daytime hours was more influential in determining oversedation than the patient's observed level of consciousness. This suggests that the oft-heard opinion that caregivers oversedate at night is an oversimplification: the actual state of the patient and the amount of sedation received has little diurnal variation, but caregivers' perceptions for what constitutes adequate sedation does change throughout the day. Given an identical patient, daytime caregivers are significantly more likely to make a judgment of oversedation compared with nighttime caregivers. An alternative explanation is that (unmeasured) characteristics of nurses that are associated with interpretation of sedation adequacy differ by day or night work status. Whether physicians have a similar diurnal bias is unknown, but clinicians should be cognizant that the work cycle of caregivers can affect the interpretation of their patient's condition.

Although Arousal and Motor Activity were associated with sedation adequacy in both statistical models, Figures 2 and 3 suggest that nurses are most likely to rate patients as oversedated when they are at the lowest scale levels of "no spontaneous movement" and unarousable with moderate tactile stimuli. On the other hand, the two highest Arousal levels greatly increase the probability of receiving an undersedation rating. This suggests that if caregivers' sedation goals are to avoid oversedation or undersedation, then using sedation scales with a few, relatively coarse, scale levels is adequate. In addition, our finding that the kinesiological state of the patient (too much spontaneous activity or too little) had the greatest influence in judging sedation adequacy suggests that unidimensional sedation scales that predominantly assess level of consciousness overlook a key behavior that strongly influences the interpretation of sedation adequacy. This study did not define whether a specific level of motor activity represented drug effect, agitation, or sleep behavior. Other factors that were not available every 4 hrs for this study, such as ventilator dyssynchrony, severity of respiratory failure, or neuro-

Table 3. Factors associated with a nurse rating of undersedation

Factor	Beta	*p* Value	Odds Ratio	95% CI
Age	0.013	<.007	1.01	1.00–1.02
Female sex	−0.114	.415	0.89	0.68–1.17
Motor Activity level	0.687	<.001	2.00	1.80–2.20
Arousal level	0.345	<.001	1.41	1.31–1.52
SIS	0.093	<.001	1.10	1.06–1.14
Daytime	−0.062	.421	0.94	0.81–1.10

CI, confidence interval; SIS, Sedative Drug Intensity Score.

Generalized estimating equations modeling for the dichotomous dependent variable "undersedation" (positive cases = 1731, with complete data for 1723 cases; compared with adequate sedation + oversedation) was performed with the inclusion of the following variables: age and SIS (continuous), sex and nighttime (dichotomous), and Motor and Arousal level (4 and 6 level-ordered, respectively). Results were similar using an autoregressive or independent covariance structure; however, due to the temporal relationship between intervals within a subject, the autoregressive structure was used for the final model. Results were similar if cases with >200 Minnesota Sedation Assessment Tool assessments were truncated, confirming that subjects who were intubated for long intervals did not unduly influence the results. Performing a manual stepwise variable entry, Motor was the most significant variable. Given Motor in the model, Arousal was the next most significant variable. Given these two in the model, SIS was most significant, and finally, given the other three variables, age was the last significant variable.

Table 4. Factors associated with a nurse rating of oversedation

Factor	Beta	*p* Value	Odds Ratio	95% CI
Age	0.008	.33	1.01	0.99–1.02
Female sex	−0.067	.750	0.94	0.62–1.41
Motor activity level	−0.103	<.001	0.33	0.23–0.48
Arousal level	−0.604	<.001	0.55	0.45–0.66
SIS	−0.122	.005	0.86	0.82–0.97
Daytime	0.877	<.001	2.40	1.87–3.09

CI, confidence interval; SIS, Sedative Drug Intensity Score.

Generalized estimating equations modeling for the dichotomous dependent variable "undersedation" (positive cases = 326 with complete data for all cases; compared with adequate sedation + undersedation) was performed with the inclusion of the following variables: age and SIS (continuous), sex and nighttime (dichotomous), and Motor and Arousal level (4 and 6 level-ordered, respectively). Results were similar using an autoregressive or independent covariance structure; however, due to the temporal relationship between intervals within a subject, the autoregressive structure was used for the final model. Results were similar if cases with >200 Minnesota Sedation Assessment Tool assessments were truncated, confirming that subjects who were intubated for long intervals did not unduly influence the results. Performing a manual stepwise variable entry, Motor was the most significant variable. Given Motor in the model, daytime was the next most significant variable. Given these two in the model, Arousal was most significant, and finally, given the other three variables, SIS was the last significant variable.

logic deficits, including delirium, may also influence sedation adequacy. Although there are other multidimensional scales that measure factors such as patient tolerance (27) or calmness (28) separately from level of consciousness, thereby more comprehensively characterizing a patient's condition, neither the MSAT nor these other scales have demonstrated superiority to unidimensional scales in managing patients.

For both opiates and benzodiazepines, continuous infusions have competing risks and benefits: they markedly decrease the likelihood of being undersedated but also increase the likelihood of being oversedated. Because method of administration was not independently associated with sedation quality (data not shown), the association between continuous infusion and sedation quality was because continuous infusions increase, two- to five-fold, the hourly dose compared with bolus therapy. This may explain the association between the use of continuous infusions and prolongation of mechanical ventilation duration (8, 29).

The distribution of patient wakefulness in this study was similar to a study by Ely et al. (22) that used a different sedation scale, but our data also show that one fifth of the time, patients exhibit no spontaneous motor activity and that there is an inverse relationship between sedation intensity and spontaneous motor activity. In a manner analogous to the trials that show increasing wakefulness during mechanical ventilation is associated with improved ICU (10, 12) and post-ICU outcomes (30), further studies should investigate the extent to which allowing increased (but noninjurious) spontaneous movement during mechanical ventilation prevents loss of muscle mass and joint function.

Because this study collected sedative data in unprecedented fine detail, it was possible to graphically show that the course of sedative therapy diverges early between survivors and nonsurvivors. In aggregate, sedative therapy declined in the second half of the intubation interval for those eventually extubated (in contrast to maintenance of sedation until just before extubation), whereas nonsurvivors had a notable increase in sedative intensity at the end, possibly due to initiating opiates or benzodiazepine infusions in anticipation of life-support withdrawal. The unexpected finding that survivors received more intense sedative therapy (per 4-hr interval) is likely confounded by the increased prevalence of impaired drug excretion and metabolic encephalopathy in nonsurvivors. In addition, the sedative dose–response relationship is altered in critically ill patients, and aggregating multiple medications into a sedative intensity score that does not adjust for changes in metabolism over time or variability in patient tolerance may affect the study results.

Limitations of the Study. When this study was conducted, the ICUs did not use sedation protocols that mandated the use of specific sedatives or an order for a numerical sedation goal. Daily sedation interruption was required only for propofol, and our data confirm that patients were most alert from 8 am to noon, when the most commonly used sedative (propofol) was given at the lowest dose. We do not know the extent to which local practice or the absence of a restrictive sedation protocol affected our conclusions. However, although randomized trials using sedation protocols have shown important clinical benefits (8–12), only about half of all ICUs document behavior with sedation scales and <20% have formal policies that call for daily sedative interruption (1–4, 6, 31).

Although our use of a novel summary drug exposure measure (sedative drug intensity score) has the advantage of aggregating across drug classes, its validity is

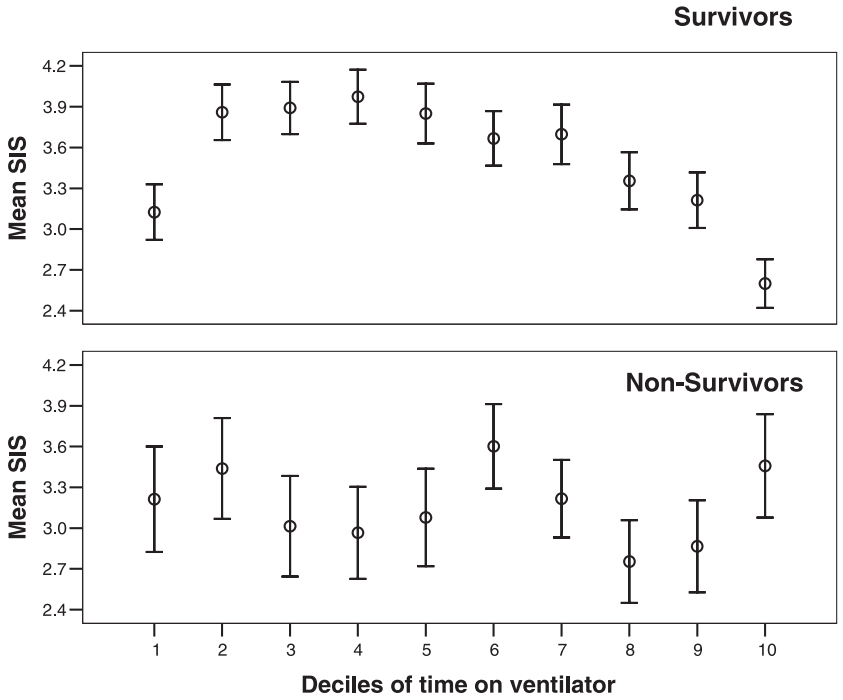

Figure 5. Trend of sedative drug intensity score (*SIS*) during mechanical ventilation. The *x-axis* is duration of mechanical ventilation divided by deciles such that the fifth decile represents the midpoint of a ventilation episode for any duration from 3 to 21 days. The *y-axis* is the mean value of the SIS within each decile. If a subject did not receive any of the eight sedative medications during a 4-hr interval, the SIS for that interval was zero. The number of SIS values for this figure was 7,089. Survivors are in the *upper panel* and nonsurvivors in the *lower panel*. *Circles* are mean values, and *bars* are 95% confidence intervals. Survivors were subjects who were extubated and alive ≥48 hrs later. Nonsurvivors died while receiving mechanical ventilation, with the common exception of a short time period when life support was removed before death.

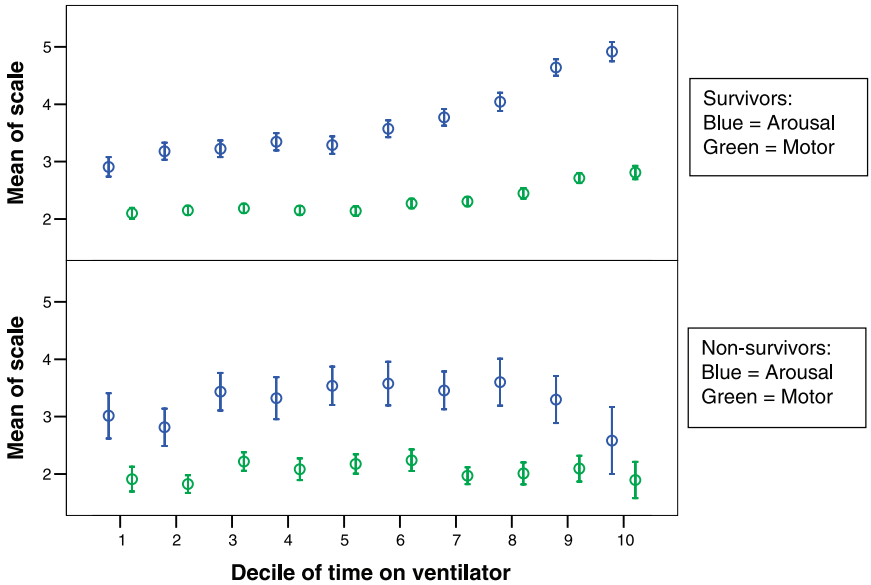

Figure 6. Trend of Arousal and Motor Activity levels during mechanical ventilation. The *x-axis* is duration of mechanical ventilation divided by deciles such that the fifth decile represents the midpoint of a ventilation episode for any duration from 3 to 21 days. The *y-axis* is the mean value of either the Arousal scale (1–6 scale in *blue*) or Motor Activity (1–4 scale in *green*) within each decile. Displayed are mean and 95% confidence interval data series for survivors (*upper panel*) and nonsurvivors (*lower panel*).

limited by the quartile ranking methodology, which assumes that a morphine dose ranked in the first quartile is equivalent to a propofol dose also in the first quartile. Our observational design, in which many patients were receiving multiple medications, makes it difficult to determine whether the dose distributions of the eight sedative medications we tested are equivalent. Similarly, we cannot determine the extent to which opiates were used to decrease responsiveness and improve ventilator synchrony (i.e., as sedatives) or as analgesics. The characterization of the participants' mean severity of illness may underestimate the actual illness severity because we used a modified Multiple Organ Dysfunction Score without the neurologic subscale. Therefore, readers should rely more on alternative measures of illness severity such as mortality, duration of mechanical ventilation, and severity of respiratory failure. We also remind readers that the ratings of sedation adequacy were from nonresearch ICU nurses directly caring for the patients and that clinicians did not use a standard method for diagnosing or treating delirium during the study interval.

CONCLUSIONS

In patients requiring mechanical ventilation, sedative therapy is widely used and nursing perception of inadequate sedation has a prevalence of 17%, with undersedation occurring five times more often than oversedation. Our data also define the multiple factors that influence nurses' judgment of sedation adequacy, including time of day and two behavioral domains (level of consciousness and spontaneous motor activity), suggesting that multiple-domain sedation scales with a few ordered levels (27, 28) more accurately characterize sedated patients than a single-domain scale with numerous levels.

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Appendix 1. Nurses' procedure for scoring the Minnesota Sedation Assessment Tool for intubated patients receiving sedative medications

1. Record highest level of *unstimulated* spontaneous motor activity observed in last 10 mins.
2. Walk to the right shoulder and observe eye opening and/or tracking.
3. If no eye opening, call first name and "Open your eyes!"
4. If no eye opening, shake right shoulder firmly and call first name and "Open your eyes!"
5. Choose the Arousal Scale category appropriate for the patient's response to procedures 2–4.
6. Judge the quality of the sedation therapy as "adequate," "oversedated," or "undersedated." Use any clinical information available in addition to the scale levels.

Motor Activity Scale

4. Movement of central muscle group(s) (back or abdominal muscles).
3. Movement of proximal limbs (hip or shoulder).
2. Movement of distal limbs or head and neck muscles.
1. No spontaneous movement.

Note: Disregard respiratory efforts, cough, swallowing, eye movement, or isolated tiny muscle contractions.

Arousal Scale

6. Eyes open spontaneously with tracking.
5. Eyes open spontaneously but not tracking.
4. Eyes closed but open to voice.
3. Eyes closed but open to shoulder shake plus voice.
2. Eyes stay closed but other patient movement observed in response to stimulation.
1. Eyes stay closed and no patient movement observed in response to stimulation.