Fluctuations in sedation levels may contribute to delirium in ICU patients

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**Background:** Delirium in patients admitted to the intensive care unit (ICU) is a serious complication potentially increasing morbidity and mortality. The aim of this study was to investigate the impact of fluctuating sedation levels on the incidence of delirium in ICU.

**Methods:** A prospective cohort study of adult patients at three multidisciplinary ICUs. The Richmond Agitation and Sedation Scale (RASS) and the Confusion Assessment Method for the ICU were used at least twice a day.

**Results:** Delirium was detected at least once in 65% of the patients (n = 640). Delirious patients were significantly older, more critically ill, more often intubated, had longer ICU stays, and had higher ICU mortality than non-delirious patients. The median duration of delirium was 3 days (interquartile range: 1;10), and RASS was less than or equal to 0 (alert and calm) 91% of the time. The odds ratio (OR) for development of delirium if RASS changed more than two levels was 5.19 when adjusted for gender, age, severity of illness, and ICU site and setting. Continuous infusion of midazolam was associated with a decrease in delirium incidence (OR: 0.38; P = 0.002).

**Conclusions:** Fluctuations in sedation levels may contribute to development of delirium in ICU patients. The risk of developing delirium might be reduced by maintaining a stable sedation level or by non-sedation.

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Conventional treatment of mechanically ventilated patients in the intensive care unit (ICU) has included deep sedation and, in some cases, muscle relaxation. Deep sedation was aimed at reducing anxiety, pain, and stress while easing adaptation to the ventilator. In the past decade, attention has increasingly focused on the downsides of deep sedation, such as prolonged mechanical ventilation and ICU stay, and particularly, the inability to assess the mental status of the patient.

An important breakthrough in sedation management was made by Kress et al. in 2000, when they demonstrated that daily interruption of continuous intravenous infusions of sedatives decreased the duration of mechanical ventilation, length of ICU stay, and length of hospital stay.¹ The authors recommended that infusions of sedatives and morphine should be restarted when patients were awake and able to follow instructions, or when patients became uncomfortable or agitated and again required sedation.

In 2010, Strøm et al. went further and tested a protocol of no sedation,² using morphine for pain management. They demonstrated the feasibility of no sedation and showed a reduction in ventilator time, ICU stay, and hospital stay. This was apparently achieved at a cost, as a higher frequency of delirium was detected in the intervention group using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition³ criteria. The method of delirium detection, however, only identified hyperactive delirium, and delirium was not among the primary end points of the study.

Sedation levels are apt to fluctuate during the ICU stay, depending on patients’ clinical condition, local practices, and ward culture.⁴ Fluctuating levels of sedation and changes in mental status are particularly evident during daily sedation interruption. Although daily interruption has been recommended internationally, it remains to be investigated whether rapid changes in consciousness (awake/sedated) might contribute to the development of delirium.
The aim of this study was to investigate the impact of fluctuating sedation levels on the incidence of delirium in ICU. Sedation level was assessed using the Richmond Agitation and Sedation Scale (RASS), and delirium was detected using the Confusion Assessment Method for the ICU (CAM-ICU). We hypothesised that major changes in sedation level might promote delirium. We defined major change as a difference of more than two levels of RASS between two consecutive assessments.

Methods

Patients
The study was a prospective cohort study at three multidisciplinary ICUs Aarhus University Hospital and Hillerød Hospital in Denmark from September 2009 to July 2011. The ICUs had 6, 10, and 12 beds, respectively, and specialist physicians present 24/7. All adult patients, 18 years and older, were included. Exclusion criteria were ICU stay less than 48 h, inability to speak Danish, and inability to communicate due to brain damage. Readmission to the ICU was counted as one admission if the patient left the ICU for less than 24 h. If patients were readmitted to the ICU (later than 24 h), only data from the first ICU stay were included in the analysis. Intensive care practices, including sedation strategy, were similar in the three units. No patients were physically restrained, and the nurse–patient ratio was 1 : 1 during daytime and 1 : 1.5 at night.

Data collection
Primary end point was the incidence of delirium. Secondary end points were ventilator days, length of ICU stay, and ICU mortality. Exposure variables were sedation level (RASS), medication status (sedated vs. non-sedated), and medication administration (bolus vs. continuous infusions).

The following data were collected from patient records: gender, age, severity of illness during the first 24 h of ICU admission [simplified acute physiology score; Simplified Acute Physiology Score II (SAPS II)], ventilator days, and use of sedative and analgesic medications. We did not record medication doses as this is subject to individual variation, but we focused on the sedation level of the patient.

All patients were assessed using the validated Danish version of the RASS and the CAM-ICU by specially trained ICU nurses at least twice a day from ICU admission to discharge (to the ward or another ICU) or death. RASS is a 10-level tool for sedation and agitation assessment ranging from −5 (unarousable) to +4 (combative), where 0 is neutral (alert and calm). CAM-ICU is used when RASS is more than −4 and detects delirium when an acute change of mental status or a fluctuating course is combined by either disorganised thinking or an altered level of consciousness.

Patients were usually assessed in the morning, afternoon, and evening. Additional assessments were performed if the patient’s mental status changed. Ongoing supervision was provided to caregivers by the first author during the entire study period to ensure consistency.

Daily delirium status was determined using the following algorithm:

- ‘Positive’ (CAM-ICU POS)
  - if at least one CAM-ICU assessment was positive
- ‘Negative’ (CAM-ICU NEG)
  - if no positive CAM-ICU and
  - at least two negative CAM-ICU or
  - one negative CAM-ICU and at least one RASS less than −2 or
  - one negative CAM-ICU and patient not present in the ICU the remaining time
- ‘Unable to assess’ (UTA)

‘Negative’ indicates neither delirium nor coma, as suggested elsewhere. We defined delirium during the total ICU stay as present if at least 1 day was positive (CAM-ICU POS) and negative if all days were negative (CAM-ICU NEG) or undetermined (UTA). We divided the CAM-ICU POS assessments into three groups according to RASS: hyperactive delirium if RASS > 0; hypoactive delirium if RASS ≤ 0; and mixed-type delirium if RASS was both > and ≤ 0 during the ICU stay. If patients were readmitted to ICU, only data from the first ICU stay were included in the analysis.

Statistical analyses
Continuous data are presented by mean and standard deviation if normally distributed, otherwise as median and 10% and 90% percentiles. Kruskal–Wallis was used to compare groups. Categorical data are presented as numbers and percentages, and Pearson’s chi-square was used to compare groups. The risk of onset of delirium was analysed as follows: each patient was followed until the first delirium positive assessment or discharge. Delirium status was assessed using logistic regression using change in RASS as the primary explanatory variable. Change in RASS was summarised as whether or not the score had changed more than two levels since

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the previous assessment. Similarly, we estimated the association between medications (sedative or analgesic agents), and administration method (bolus vs. continuous), and the risk of delirium onset since the previous assessment. We report estimates both unadjusted and adjusted for gender, age (in quartiles), SAPS II, ICU site (ICU-1, ICU-2, ICU-3), and ICU setting (medical/surgical). Results were considered significant if the \( P \) value was less than 0.05. All calculations were performed using StataCorp (2011), Stata Statistical Software: Release 11 (StataCorp LP, College Station, TX, USA).

**Ethics**

The study protocol was approved by the Danish Data Protection Agency (journal number 2007-58-0010) and the National Health Service of Denmark (journal number 7-604-04-2/226/KWH). According to the Regional Research Ethics Committee, the study required no approval because no interventions were performed. The ClinicalTrials.gov number is NCT01291368.

**Results**

**Demographics**

Flow diagram of the study and patient characteristics are presented in Figure 1 and Table 1. The mean ICU length of stay was 10 days. At enrolment, 48% of the patients were on mechanical ventilation. Delirious patients were significantly older and had higher SAPS II scores and worse outcomes than non-delirious patients (Table 1). Out of the total number of ICU days (6427 days) in our study, patients were delirious and coma negative in 45%, delirium positive in 20%, and comatose in 35%. The median duration of delirium was 3 days, interquartile range 1;10. Out of 3544 delirium positive scores, RASS was 0 or less in 69% (Fig. 2). Out of the 419 delirium positive patients, 40% had hypoactive delirium, 12% had hyperactive delirium, and the remaining 48% were identified with mixed delirium.

Only 20% of the 419 delirious patients had more than 10 CAM-ICU POS assessments, 45% had fewer than four, and 18% had only one. At ICU admission, 41 patients were already delirious at admission to the ICU; these patients are not included in the following analysis of sedation level and medications prior to first CAM-ICU POS.

The odds ratio (OR) for the onset of delirium from a stable RASS to a RASS with changes of more than two levels (major changes in sedation level) was 5.19 (\( P < 0.001 \)) when adjusted for gender, age, SAPS II, and ICU site and setting (Table 2). We found that any change in RASS was significantly associated with the onset of delirium (data not shown).

**Sedative agents**

The 640 patients eligible for the study did not receive bolus or infusion of sedatives during 71% of the 6427 days. Among 599 patients (excluding patients delirious on admission), propofol was used in 27%, midazolam in 14%, combination of propofol and midazolam in 3%, and no sedation in 56% of the days before the first CAM-ICU positive assessment.
The administration of continuous infusions of midazolam was associated with a significant decrease in delirium positive assessments (OR: 0.38, P = 0.002) compared with other sedative agents, other administration methods, or no sedation (Table 2).

**Analgesic agents**
Delirium onset (number of days before first CAM-ICU POS) was associated with the use of alfentanil (OR: 1.53, P = 0.017), while delirium onset was unaffected by other analgesics (Table 2).

**Discussion**
The aim of our study was to investigate the impact of fluctuating sedation levels on the incidence of delirium in ICU, and our main finding was a significant association between major changes in sedation level and incidence of delirium. A secondary finding was the high incidence of delirium in our population (65% delirium positive at least once), which is supported by other studies involving medical and surgical critically ill patients.10,11
Fluctuations in sedation level are bound to occur during an ICU course in relation to the condition of the patient and therapeutic interventions requiring sedation. The benefits of daily interruption of sedation described by Kress et al. in 2001 did not take the risk of delirium into account. The more recent study by Strøm et al. in 2010 describing a protocol of no sedation found a higher incidence of delirium in the non-sedated group of patients, but only hyperactive delirium was recorded. In our study, using the CAM-ICU, we detected hypoactive, hyperactive, and mixed-type delirium, which suggests that a proportion of the sedated group in the study by Strøm et al. might have had undetected hypoactive or mixed-type delirium. Thus, it is important to use a validated instrument for delirium detection that is sensitive to all types of delirium.

In a randomised study, daily interruption of sedatives prior to spontaneous breathing trials (SBT) showed no variation in delirium days. According to our findings, the delirium status after daily awakening may have an impact on the success of the SBT, as major fluctuations in sedation level was found to contribute to delirium. We recommend that future studies take this into account when weaning from mechanical ventilation. We argue that if the sedation level is managed to avoid sudden major fluctuations and promote a more gradual awakening, weaning might be facilitated and perhaps some incidents of delirium prevented.

Our study indicates that delirium incidence increases with the length of ICU stay, which is corroborated by other studies. This finding might be related to major changes in sedation level or number of sedation interruptions.

In a previous study of delirium in Danish ICUs, delirium was detected in only 40% of the patients as opposed to 65% in the present study. The higher rate of delirium in our study could be the result of better assessment methods or lighter sedation, as hypoactive delirium could have been underdetected in the earlier study. This confirms our assumption that hypoactive delirium may go undetected if patients are not carefully assessed by specially trained staff using a validated instrument.

Our study showed that midazolam was associated with fewer incidents of delirium than propofol. This was at odds with a study in 2008 that demonstrated midazolam to increase OR for delirium up to 3.22 in contrast to 0.61 in our study. The inconsistent findings regarding the association between midazolam and delirium might be explained by drug accumulation and slower response during sedation interruption. Another factor in our study was the circadian variation of delirium. If sedation interruption is affected mostly during daytime and delirium is predominant during night, some delirium might go undetected, unless patients are assessed systematically around the clock. Recent years have shown a trend towards analgo-sedation, where pain is addressed before sedation. We were unable to explore this trend in our study because many patients went without analgesia, which might have increased the incidence of delirium. Our recommendation is to ensure sufficient analgesia by systematic pain assessment with a validated instrument.

Study limitations and strengths
Sedation regimes might have evolved towards lighter sedation during the 2 years of our study. Pain was not assessed in this study, limiting our information regarding the association between alfentanil and delirium level. Alfentanil was primarily used as a preventive measure before patient mobilisation, which might have influenced the results; however, other opiates were used preventively as well.

A major strength of our study was the systematic delirium screening. We eliminated false negative scores by excluding patients with fewer than two negative CAM-ICU assessments daily. A second strength of our design was the use of bedside nurses for patient assessment, as they were with the patients around the clock. This provided an opportunity to study the implications of fluctuating sedation levels. Finally, the assessment of sedation level rather than medication dosage could be considered a strength because of the large inter-individual variation of effective doses in different patients.

Conclusion
Major changes in sedation level were associated with the onset of delirium in our study. Dosage, administration, timing, and choice of sedative agent may potentially influence delirium status in ICU patients. The risk of developing delirium might be reduced by maintaining a stable sedation level or by non-sedation. We recommend systematic delirium assessment using a validated instrument to prevent, detect, or treat ICU delirium. Future studies are recommended to explore associations between medications and incidence of delirium.

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