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Intensive care unit syndrome/delirium is associated with anemia, drug therapy and duration of ventilation treatment

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Background: We have performed a prospective qualitative investigation of the ICU syndrome/delirium; the main parts of which have recently been published. The aim of the present study was to explore the relationship between the ICU syndrome/delirium and age, gender, length of ventilator treatment, length of stay and severity of disease, as well as factors related to arterial oxygenation and the amount of drugs used for sedation/analgesia.

Methods: Nineteen mechanically ventilated patients who had stayed in the ICU for more than 36 h were closely observed during their stay, and interviewed in depth twice after discharge. Demographic, administrative and medical data were collected as a part of the observation study.

Results: Patients with severe delirium had significantly lower hemoglobin concentrations than those with moderate or no delirium ($P=0.033$). Patients suffering from severe delirium spent significantly longer time on the ventilator and at the ICU, and were treated with significantly higher daily doses of both fentanyl ($P=0.011$) and midazolam ($P=0.011$) in comparison with

those reporting only moderate or no symptoms of delirium. There were no significant differences in the Therapeutic Intervention Scoring System scores, reflecting the degree of illness, between patients with and without delirium.

Conclusion: The development of the ICU syndrome/delirium seems to be associated with decreased hemoglobin concentrations and extended times on the ventilator. Prolonged ICU stays and treatment with higher doses of sedatives and opioids in patients with delirium appear to be secondary phenomena rather than causes.

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Key words: arterial oxygenation; critical and intensive care; hemoglobin; ICU syndrome/delirium; length of stay; opioids, sedatives.

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THE INTENSIVE Care Unit syndrome (ICU syndrome/delirium) (1) is a well-known problem in intensive care patients. It has been shown that acute confusion or delirium, especially in elderly patients, increases the length of hospital stay (2, 3), as well as mortality (4).

The prevalence of delirium in critical care units varies considerably, ranging from 2 to 57% (3, 5, 6, 9). These great variations may well be a result of inconsistent definitions of delirium and because different patient populations have been studied. The quality of evaluation of the patient's mental status is also important. Thus, it has been reported that the incidence of mental disturbances among intensive care patients in reality seems to be higher than is routinely documented in the records (10, 11).

The pathogenetic mechanisms of the ICU syndrome/delirium are not well understood and the matter is still controversial (6–8). However, according to

Kuch (12), the syndrome's development seems to depend on a complex interaction between the patient's previous psychological problems, the psychological trauma inflicted by the illness, the stress induced by the environment and the ICU's treatment and care. Moreover, various physical factors related to abnormal blood biochemistry values and drugs affecting the functions of the brain appear to be important.

We have performed a prospective investigation of the ICU syndrome/delirium by means of qualitative methodology, including observations (13) and patient interviews (14, 15), to correlate the appearance of the syndrome with the patient's own experiences of being acutely confused. As a part of the observation study (13), data including age, gender, length of ventilator treatment, length of stay, severity of disease as well as factors related to arterial oxygenation and amount of drugs used for sedation/analgesia were collected. The aim of the present study was to examine the influence

of these factors on the development of the ICU syndrome/delirium as it emerged from our qualitative studies (13–15). Thereby shedding some light on two related and evident questions: is the ICU syndrome/delirium itself a primary cause in escalating the need for opioids and sedatives, which consequently prolong the duration of mechanical ventilation and ICU stay? Or is the development of the ICU syndrome/delirium rather secondary to the use of central nervous system active drugs?

Methods

Study protocol

Our investigation of the ICU syndrome/delirium consisted of two parts: observation and interview. The main results have already been published (13–15). The investigation also included a collection of administrative, demographic and medical data. The period of data collection was between 1st February and 20th May 1995 and between 20th August and 30th November 1995. The ICU ward was a regional hospital's (south Sweden) general ICU, in which, other than patients requiring cardiac- or neurosurgery, seriously ill patients with both surgical and medical diagnoses received treatment and care.

Ethical considerations

The Regional Committee for Medical Research Ethics at Lund University, Sweden approved the study. Before the patient observations were performed, informed consent was obtained from a close relative, and regarding the interview, was obtained directly from the patient (15).

Patient selection

A total of 31 patients, 20 males and 11 females, who were mechanically ventilated and had stayed in the ICU for more than 36 h were eligible for inclusion (14, 15).

Exclusion criteria included: unconscious patients admitted after head trauma, cardiac arrest, metabolic- or drug-induced coma, patients addicted to alcohol and/or CNS active drugs or with a history of psychiatric diseases, severe loss of hearing, and not Swedish speaking.

Interviews and observations

The methods used in the observation and interview studies are only briefly presented (for details see 13–15). The patients were observed during the weaning process and during the days following extubation. Two interviews per patient were planned. The first in-

terview usually took place on the general ward between 6 and 10 days after discharge from the ICU. The second interview took place 4 to 8 weeks after the first interview, mostly in the patient's home. Interpretations and analysis of the text from the interviews comprised the data analyses. After the interviews were compiled, an analysis of the observations was started. A flow chart for each patient's reactions, behavior, environmental circumstances, and interactions with the staff was constructed for the observations made during the weaning process until the third day following the day of extubation. In this way each patient's individual courses could be followed, documented, and compared with their interview results (14, 15). Two patients died before they could be interviewed, and four did not regain an acceptable level of consciousness within a week after discharge. Six patients were interviewed only once. Of these, two refused further participation in the study and four stated that they could not recall their ICU stay. Thus, 19 patients were observed, and interviewed twice as planned (13–15).

Administrative and medical data

Demographic factors, medical/surgical reasons for admission to the ICU, length of ventilator treatment, Therapeutic Intervention Scoring System (TISS) scores (16), length of stay and different medical data were collected as a part of the observation study. The researchers did not interfere with the routine ICU management of the patients.

The following medical data were recorded:

- 1 During the ICU stay, the lowest daily value measured of arterial oxygen tension (PaO₂), arterial oxygen saturation (SaO₂), arterial oxygen content (CaO₂, calculated as hemoglobin content × SaO₂ × 1.34) and serum hemoglobin.
- 2 The highest and lowest daily value of arterial carbon dioxide tension (PaCO₂), as well as the highest daily value of serum creatinine.
- 3 The mean daily total dose of midazolam (mg 24h⁻¹; Dormicum®) and fentanyl (mg 24h⁻¹; Leptanal®).

Statistics

The Kruskal–Wallis test and the Mann–Whitney *U*-test were used for statistical comparisons between the subgroups of patients for medical continuous data. Categorical data was calculated using the Chi-square test or, if there were insufficient number of patients, using Fisher's exact test. A *P*-value of less than 0.05 was considered statistically significant. Multiple logistic regression was used to determine the independent associations of blood biochemical factors, drug doses

and administrative data, but because of an insufficient number of patients in the different groups and because of the very large interindividual data variations it was not found to be useful. All group data are given as medians (min.–max.) unless otherwise stated.

Results

As reported earlier (13, 14), the results of the observations and those of the patient interviews were explicitly concordant regarding the development and appearance of delirium. Based on the severity of the signs and symptoms of the ICU syndrome/delirium the group of 19 patients were classified into the following three distinctly different groups (for details see 13, 14, 17).

Severe ICU syndrome/delirium (group SD)

Six patients had a fully developed and severe delirium lasting several days. The patients showed an agitated behavior, and reported very disturbing, bizarre and fearful unreal experiences with feelings of chaos, disturbed sleep and loss of control, starting already at return to consciousness.

Moderate ICU syndrome/delirium (group MD)

Eight patients had a moderate delirium with a few, but reiterating unreal experiences, which developed during the days immediately following extubation. The patients appeared normal most of the time, but showed short bursts of restlessness with incoherent and mumbling speech. They experienced some level of fear and uneasiness.

No ICU syndrome/delirium (group ND)

Five patients had no signs of delirium or only slight symptoms of short-lasting confusion, such as time and place disorientation.

Administrative and demographic data

There were no statistically significant differences between the groups in age or TISS (Table 1). The total group of patients ($n=19$) consisted of 13 males and six females. There was a statistically significant overrepresentation of females in the group that experienced no delirium (group ND). Patients who suffered from severe delirium (group SD) had a significantly longer duration of ventilator treatment and ICU stay than patients in the other two groups.

Variables related to arterial oxygenation

Biochemical variables describing the arterial blood's degree of oxygenation are shown in Fig. 1. The lowest daily value of each variable recorded during the patient's ICU stay was identified, and the medians for each group were calculated. Patients who suffered from severe delirium (group SD) had significantly lower hemoglobin concentrations than both the moderately delirious (group MD) and non delirious (group ND) patients ($P=0.033$). There was a tendency towards a similar but less significant ($P=0.071$) difference in PaO_2 between the groups. There were no other statistically significant differences between the groups in any other variables related to arterial oxygenation.

Arterial blood carbon dioxide tension

The lowest as well as the highest daily PaCO_2 values measured during the patient's stay in the ICU were identified, and the medians for each group were calculated (Fig. 1). There were no statistically significant differences in these two variables between any of the groups.

Blood creatinine concentration

The highest daily concentration of creatinine noted in each patient's record was identified, and the median for each group was calculated. The values (mmol l^{-1} ;

Table 1

Clinical characteristics.				
	Severe delirium ($n=6$)	Moderate delirium ($n=8$)	No delirium ($n=5$)	Significance level
Age (years)	70 (35–82)	72 (23–81)	63 (34–74)	NS
Gender (M/F)	4/2	8/0	1/4*	$P=0.007$
Length of ICU stay (h)	324** (120–552)	81 (46–216)	120 (60–144)	$P=0.005$
Duration of ventilation (h)	222** (106–384)	24 (12–124)	18 (12–41)	$P=0.001$
TISS (points)	32	34	35	NS

*Significantly different from moderate delirium (Fisher's exact test); **Significantly different from moderate delirium and no delirium (Kruskal-Wallis and Mann-Whitney U -test).

Medians (min.–max.) are shown; NS, not significant.

TISS, Therapeutic Intervention Scoring System; ICU, intensive care unit.

median and min.–max.) of group SD, MD and ND were 94 (77–153), 189 (67–239) and 105 (52–167), respectively. There were no statistically significant differences between the groups.

Treatment with opioids and sedatives

With a few exceptions, fentanyl and midazolam were used for analgesia and sedation. Figure 2 shows that patients who developed severe delirium had received significantly larger daily doses of both fentanyl and midazolam than those who suffered from moderate delirium or had no delirium or only slight symptoms of confusion.

Discussion

The present study is a part of a prospective investigation of the appearance and development of the ICU syndrome/delirium, which is mainly based on quali-

tative methodology. The observation results and patient interviews have already been published (13–15). This study focuses on the putative associations between some basic demographic, administrative and medical factors and the development of the ICU syndrome/delirium.

Our investigation has evident limitations. The strict exclusion criteria and relatively high morbidity and mortality rates, resulted in only 19 patients being observed and interviewed twice, as required by the qualitative study's design (14, 17). Nevertheless, the observation and interview results were congruent (13). Based on the ICU syndrome/delirium's severity of signs and symptoms, the patients, although small in number, could be classified into three clearly different groups, i.e. those with severe delirium, moderate delirium and no delirium (13, 15, 17).

The 13 males and six females studied were considered rather old, with a median age approximately

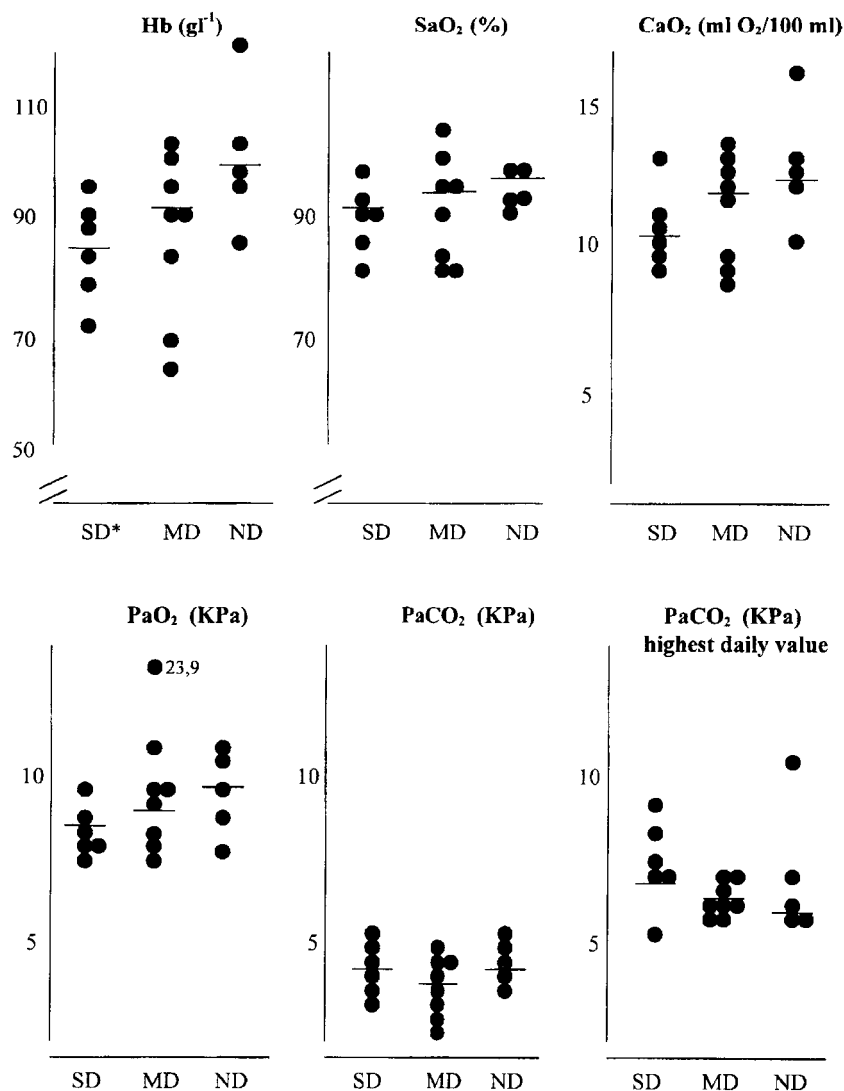


Fig. 1. Haemoglobin values and arterial blood gas parameters in patients with severe delirium (SD), moderate delirium (MD), and no delirium (ND). Each dot represents the individual patient's lowest daily value, except for PaCO₂ (highest daily value). Horizontal bars denote median values within groups. * $P=0.033$ compared with MD and ND groups. There were no other significant differences between the groups of patients (Kruskal–Wallis and Mann–Whitney U-test).

70 years. Females were over-represented in those patients who had no ICU syndrome/delirium signs, while males dominated in the groups that developed the syndrome. The population was too small, however, to allow any meaningful conclusion to be drawn from this finding.

We also found that patients who experienced the most severe form of delirium had spent significantly longer on the ventilator and at the ICU than those experiencing moderate or no delirium symptoms. Furthermore, the patients with severe delirium were treated with significantly higher daily doses of both fentanyl and midazolam. Theoretically, two fundamental questions are raised: Is the ICU syndrome/delirium a primary cause, which escalates the need for opioids and sedatives, which prolongs the duration of mechanical ventilation and their stay at the ICU? Or is the development of the ICU syndrome/delirium a consequence of the use of high doses of fentanyl and midazolam? Evidently, because of the small sample size, it is difficult to draw any firm conclusions from our study concerning causal relationships between various factors recorded and the delirium's development. Nevertheless, the patients who developed the most severe form of delirium had their first signs and symptoms early in their ICU stay (13, 14). This supports the theory

that the ICU syndrome/delirium is an early phenomenon (3, 18). Thus, there are some indications that the appearance of the ICU syndrome/delirium, including agitated behavior *per se*, could have been a reason behind the use of large doses of midazolam and fentanyl, which indirectly prolonged the duration of mechanical ventilation and the stay at the unit. On the other hand, it is well known that psychoactive drugs such as benzodiazepines and opioids are associated with postoperative delirium (5, 10, 19). Accordingly, it cannot be excluded that the development of the ICU syndrome/delirium in our patients, in some way or another, was also linked to the use of midazolam and fentanyl.

Factors related to arterial oxygenation, such as blood hemoglobin concentrations and to a certain extent PaO₂, were significantly more reduced among the patients with delirium. This is in concordance with findings from recent studies on the postoperative confusion or delirium; a phenomenon closely resembling the ICU syndrome/delirium (20). Hence, it has been shown that postoperative delirium is associated with factors such as postoperative hematocrit (20), postoperative hypoxemia (21, 22), and respiratory complications (23). If there were a true association between decreased hemoglobin content and delirium, one could argue that the current trend in critical care to accept lower hematocrit and hemoglobin values than before (24) would increase the risk of the ICU syndrome/delirium's development.

It seems reasonable to presume that metabolic consequences of renal insufficiency or hyper- or hypocarbia could influence the development of the ICU syndrome/delirium by interfering with the cognitive function of the brain (25). This possibility, however, is not supported by our study, because neither the highest daily value of blood creatinine concentration nor the highest or lowest daily value of arterial carbon dioxide tension seemed to be associated with the delirium's appearance.

Were the patients who developed delirium simply sicker than those who had no signs of delirium? The findings associating the delirium's appearance with a significantly reduced hemoglobin concentration, impaired arterial oxygenation, a longer time on the ventilator and a longer duration of ICU stay, as well as the use of very high doses of sedatives and opioids, might strengthen this opinion. We were, however, unable to show any differences between patients with and without delirium with regard to the average TISS score, which reflects the intensity of care and thus, to some extent, the degree of illness (16).

In conclusion, our study, although clearly limited by its small number of patients, provides some evidence

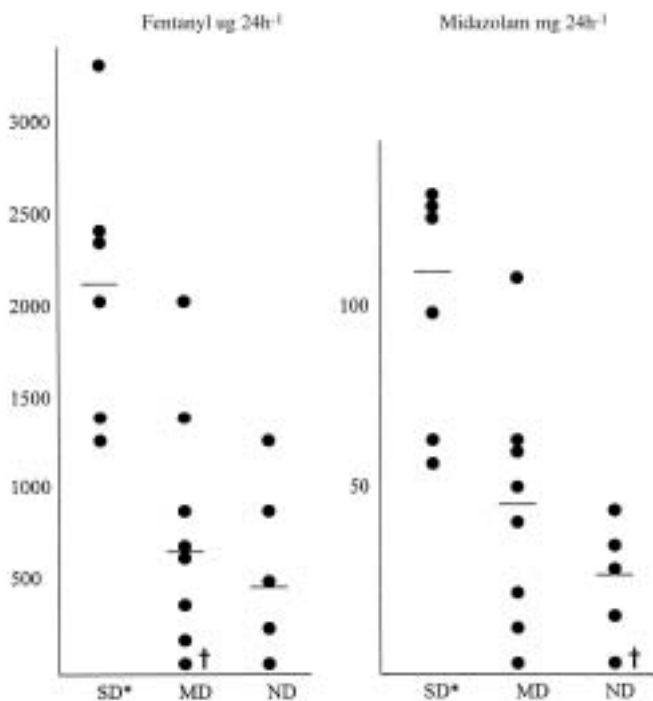


Fig. 2. Mean daily dose of fentanyl and midazolam in patients with severe delirium (SD), moderate delirium (MD), and no delirium (ND). Horizontal bars denote median values within groups. * $P=0.011$ compared with MD and ND groups (Kruskal–Wallis and Mann–Whitney U-test). †Patients had no fentanyl or midazolam.

in understanding the importance of various basic clinical factors in the development of the ICU syndrome/delirium. Patients who developed a severe ICU syndrome/delirium showed greater reductions of hemoglobin concentration, used higher daily doses of benzodiazepines and opioids, had longer durations of ventilator treatment and ICU stays than those who had no delirium or only moderate delirium. Those who developed severe delirium showed signs and symptoms soon after their return to consciousness. This may indicate that the ICU syndrome/delirium is an early phenomenon, and that high doses of sedatives and analgetics, prolonged ICU stays and longer ventilator treatments in patients with severe delirium might be secondary phenomena rather than causes.

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