

Delirium in the intensive care unit: searching for causes and sources

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It is well known that many patients admitted to the intensive care unit develop delirium, with the incidence reported as 20% to 85% of admissions.¹ The sequelae of delirium are often significant in terms of prolonged length of stay in both the ICU and hospital and increased morbidity and mortality.² This has an impact not only on patients and their families, but also on health care resources. Despite a marked increase in interest in the topic, with a multitude of identified aetiologies and treatment suggestions, no established pathological basis, diagnostic indicator or proven treatment has been found to date.^{3,4}

Recently, several authors have proposed an interaction between the immune system and both physical and psychological stress, with the immune system activated in response to stress to restore homeostasis.⁵ While minor stress does not harm the body and may stimulate further immune activity, exposure to prolonged stress suppresses immune function, escalating the severity of illness. Many critically ill patients are at risk of immune suppression because of trauma, sepsis and also the psychological stress associated with admission to the ICU, where sleep deprivation, anxiety and pain are common.^{6,7}

Psychological and psychiatric comorbidities such as delirium have been described in patients with end-stage renal failure, both those not yet receiving haemodialysis and those already on haemodialysis. Haemodialysis has been associated with dialysis disequilibrium syndrome, dialysis dementia and progressive intellectual dysfunction.^{8,9} Rates of delirium have been quoted as 1%–5% for patients receiving long-term haemodialysis,¹⁰ but delirium associated with short-term use of continuous venovenous haemodiafiltration (CVVHDF) within the ICU is less substantiated.¹¹

Currently, delirium scales are the only means for diagnosing delirium.¹²⁻¹⁴ Although these scales have been formulated specifically for use in the ICU, they have limitations and cannot be used for comatose patients.¹⁵ Identification of biochemical predictors of delirium could assist in patient assessment, intervention and follow-up. Our study examined the relationship between various physiological markers and the presence of delirium in a cohort of ICU patients who had been screened prospectively using a delirium scale.

ABSTRACT

Introduction: Currently, diagnosis of delirium in the intensive care unit requires the use of one of a range of screening scales. Publications on delirium in the ICU are increasing, but most focus on psychological markers, with only limited data on physiological indicators of delirium.

Aim: To assess the relationship between a range of physiological and treatment markers and the presence of delirium in an ICU cohort.

Methods: Patients admitted to the ICU of a metropolitan tertiary hospital between 1 August 2002 and 31 January 2003 were prospectively screened for delirium using the Intensive Care Delirium Screening Checklist (ICDSC). A retrospective chart review was undertaken to identify potential markers: raised white cell count, neutrophil count, and serum C-reactive protein concentration, lactic acidosis, low haemoglobin concentration, use of inotropic support, corticosteroids, or continuous venovenous haemodiafiltration (CVVHDF), and presence of systemic inflammatory response syndrome. Association of these markers with delirium was assessed using χ^2 statistics.

Results: Of 56 ICU patients who were screened for delirium, charts could be retrieved for 44 (80%): 21 had delirium during the ICU admission, and 23 did not. CVVHDF was the only variable associated with an increased risk of delirium ($P=0.03$).

Conclusions: Treatment with CVVHDF was the only factor associated with the presence of delirium. Further research is warranted into physiological indicators as adjuncts to psychological assessment scales for delirium. The quest to find a simple biomarker for delirium continues.

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Methods

Design

The study was a retrospective chart review that sought physiological markers of delirium in patients who were prospectively screened for delirium. The study was registered as a quality improvement activity before the chart review was performed and thus did not require ethics approval.

Table 1. Associations between delirium and baseline variables

Baseline variable	Delirium (n = 21)	No delirium (n = 23)	P*
Male	14 (67%)	12 (52%)	0.33
Survived to hospital discharge	16 (76%)	20 (87%)	0.36
Inotrope treatment	15 (71%)	12 (52%)	0.19
Corticosteroid treatment	8 (38%)	9 (39%)	0.94
SIRS	13 (62%)	14 (61%)	0.94
White cell count high [†]	17 (81%)	13 (57%)	0.08
Neutrophil count high [†]	17 (81%)	16 (70%)	0.38
Lactic acidosis in absence of CVVHDF [‡]	14 (67%)	16 (70%)	0.84
Haemoglobin low [†]	19 (91%)	18 (78%)	0.27
CVVHDF	6 (29%)	1 (4%)	0.03
C-reactive protein raised [†]	2/19 (11%)	4/16 (25%)	0.38 [§]

* P values were calculated from χ^2 test statistics for all variables except raised C-reactive protein.

[†] Definitions: white cell count high, $> 12 \times 10^9$ cells/L; neutrophil count high, $> 9 \times 10^9$ cells/L; haemoglobin low, < 80 g/L; C-reactive protein raised, ≥ 50 mg/L.

[‡] Patients who underwent CVVHDF were excluded from the analysis of lactic acidosis. This ensured that any elevated level of lactic acid was an expression of the patient's metabolic state and not the result of lactate having been added to the dialysate.

[§] Nine patients were missing data on C-reactive protein. Comparison was by Fisher's exact test, as the small numbers made the χ^2 test inappropriate.

SIRS = systemic inflammatory response syndrome.

CVVHDF = continuous venovenous haemodiafiltration. ◆

Setting and participants

Participants comprised all 56 patients admitted to the ICU of a metropolitan tertiary hospital between 1 August 2002 and 31 January 2003 who fulfilled the inclusion criteria: age > 18 years, no neurological abnormality present on admission, ICU admission ≤ 96 hours, and provision of informed consent. Participants were prospectively screened twice daily for delirium using the Intensive Care Delirium Screening Checklist (ICDSC).¹² This screens for fluctuations in thought process consistent with delirium, using an eight-item checklist: level of consciousness, inattention, disorientation, hallucinations, psychomotor activity, speech or mood, sleep disturbances and fluctuating symptoms. This scale has shown 99% sensitivity and 64% specificity.¹² In our study, 25 patients showed signs and symptoms consistent with delirium during their ICU admission, and 31 patients did not display these signs and symptoms.¹⁶

Chart review and data analysis

The charts of the screened patients were retrieved and reviewed by one of the authors (BLR), who was blinded to the results of ICDSC screening. For each day of ICU

admission, data on the following clinical markers were collected: haemoglobin (Hb) concentration, white cell count (WCC), neutrophil count, serum C-reactive protein and lactic acid concentrations, and data required to identify systemic inflammatory response syndrome (SIRS).¹⁷ The diagnosis of SIRS requires two or more of the following criteria:

- temperature $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$;
- heart rate > 90 beats per minute;
- respiration > 20 breaths per minute or $\text{PaCO}_2 < 32$ mmHg; and
- WCC $< 4 \times 10^9$ cells/L or $> 12 \times 10^9$ cells/L, or $> 10\%$ immature (band) cells.

The overall use of corticosteroids, inotropic support and CVVHDF were also recorded, as was demographic information, such as age, sex and hospital outcome (alive or dead). These variables were chosen for their ease of measurement and widespread availability in the acute care setting, and as an extension of variables previously studied in the literature.

Continuous variables were categorised as either normal or abnormal. Associations between delirium and all variables were assessed using χ^2 tests. A P value less than 0.05 was regarded as statistically significant.

Results

Of 56 patients prospectively screened for delirium using the ICDSC, charts were able to be retrieved for 44 (80%). These comprised 21 of the 25 patients identified as having delirium and 23 of the 31 identified as not having delirium during their ICU admission.

Table 1 shows the univariate associations between delirium and collected measurements. The risk of developing delirium was higher among patients requiring CVVHDF ($P = 0.03$). There were no significant statistical associations with any of the remaining variables tested.

Discussion

The quest to find a biomarker for easy and rapid identification of delirium among critically ill patients continues. Most publications on delirium in the ICU relate to the psychological aspects of the ICU stay, such as sensory deprivation, pain and immobility.¹⁸ There are few clinical trials on the prevention of delirium, and many reviews base their work on hypothesis.¹⁹⁻²¹ Studies of the relationship between the development of delirium and physiological markers are extremely limited and often hampered by retrospective delirium assessments and chart reviews.²² Assessment scales may be impossible to apply in critically ill patients because of factors such as coma and deep sedation. However, it is not inconceivable that comatose and deeply sedated

patients suffer delirium without any means of assessing the risks. The appropriateness of delirium assessment scales in the ICU has also been debated in the literature; hence, there is a dearth of available tools for prognostication and diagnosis of delirium in the ICU.⁴

The strength of our study is that it assessed a predefined cohort of patients who were prospectively screened for delirium during their ICU stay.¹⁶ However, as the sample size was small, this retrospective study may be underpowered to detect subtle associations. Its size was limited by the size of the study from which it drew its participants, and it may thus be best viewed as a pilot study.

Our previous study of the incidence of delirium in the ICU reported on clinical variables that included APACHE II and SOFA scores, ventilation, and ICU and hospital length of stay. It concluded that only ICU length of stay was a statistically significant indicator for the development of delirium.¹⁶

Continuous venovenous haemodiafiltration

Our results show that patients who underwent CVVHDF had a significantly higher risk of developing delirium. In a study by Levy et al into development of acute renal failure after administration of radiographic contrast material, 24% of patients with acute renal failure developed acute mental status changes, versus 13% of those without acute renal failure.¹¹ Brown and Brown described how renal failure is associated with many subtle, and several distinct, alterations in neuropsychiatric function.²³ This was echoed by Fukunishi et al, who found the incidence rate of "whole psychiatric disorders" to be 11%.²⁴ However, these two reports referred to end-stage renal failure outside the critical care setting. Haemodialysis has been associated with dialysis disequilibrium syndrome, dialysis dementia and progressive intellectual dysfunction.^{8,9} Rates of delirium of 1% to 5% have been reported for patients undergoing long-term dialysis therapy, but an association between delirium and short-term CVVHDF within the critical care setting has not been established.¹⁰ Whether delirium is related to the underlying renal failure or to the use of CVVHDF is difficult to further define. Thus, from this study, we conclude that critically ill patients who receive CVVHDF may be predisposed to developing delirium. This needs to be borne in mind, but should not preclude the administration of CVVHDF.

Haemoglobin concentration

Seaman et al demonstrated that a low premorbid Hb concentration was more frequent in patients who developed delirium than in the non-delirious group.²² They examined a larger cohort of 101 ICU patients, but the raters were not blinded to the delirium score and performed this

scoring retrospectively, in contrast to our study, where delirium scoring was prospective.²² Granberg et al drew a similar conclusion to Seaman et al, with delirious patients displaying a significantly lower Hb concentration, thereby highlighting the importance of optimising oxygen transport and considering the current threshold for blood transfusion.²⁵ However, these observations were not matched in our study.

Inflammatory markers: white cells, neutrophils, and C-reactive protein

Delirium is commonly associated with local or systemic infections, although a clear association between inflammatory markers and delirium is yet to be established. Uhlig and Kallus reviewed the literature for interactions between behaviour and the immune system, but failed to establish whether the signs of inflammation were due to psychological aspects (pain, agitation and hallucination) or physical aspects of illness.⁷ In our study, an elevated WCC was weakly associated with delirium ($P=0.08$), but the relationship did not reach significance. There was no difference between the delirious and non-delirious groups in other markers of infection, such as neutrophil counts and C-reactive protein concentration.

Corticosteroid therapy

Psychological responses to corticosteroid administration are controversial. Some evidence points to reduced stress exposure and improved long-term quality of life with the administration of hydrocortisone.^{26,27} Yet, in other studies, delirium has been shown to account for around 13% of the psychological symptoms associated with steroid use, and to increase in incidence with higher doses.²⁸

However, our study did not demonstrate any difference in steroid therapy between delirious and non-delirious patients. Steroids are prescribed in the ICU predominantly to patients with sepsis. However, sepsis accounted for only 5% of all admissions to our ICU. Thus, in view of the overall number of participating patients ($n=44$), the indication for prescribing steroids would most likely have exceeded the sepsis cohort.

Seaman et al used sepsis and pneumonia as a measure of oxidative stress, and found that patients with sepsis developed delirium more frequently than those without sepsis.²² However, ICU patients with sepsis are among the sickest of the ICU population and consequently are already more prone to developing delirium.

Biochemical markers

For a biomarker to be useful in predicting delirium, it needs to be simple and widely applicable, such as a blood test that can be preformed rapidly in any laboratory and repeated

daily. Nakamura et al measured the levels of plasma free-3-methoxy-4-hydroxyphenyl (ethylene) glycol and found that elevated preoperative levels were a predictor of postoperative delirium.¹⁰ However, as these measurements require specialised laboratories, the search for a simple biochemical marker continues.

Conclusions

Our study demonstrated a relationship between the development of delirium and treatment with CVVHDF. While this should not preclude use of CVVHDF in patients with renal failure, the relationship needs to be borne in mind by health professionals. A strength of our study was that the cohort was prospectively screened for delirium. However, it would be desirable to repeat the study in a larger cohort of patients to identify more subtle relationships.

The search continues for a simple marker to predict delirium which can be used as an adjunct to routine delirium assessment and screening, particularly in patients who are comatose or deeply sedated, and thus cannot be assessed using conventional delirium scales.

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