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Critical Care Update

Delirium

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Patients in critical care units are managed with many interventions, such as mechanical ventilation and endotracheal intubation, that are perceived to be distressing. Pain is a common memory of patients from their intensive care unit (ICU) stay. Agitation may precipitate accidental removal of endotracheal tubes or intravascular catheters used for monitoring or the administration of medications. Consequently, sedation and analgesia are common therapies for patients in the ICU. Although pain must be treated adequately, evidence from randomized controlled trials consistently supports the use of the minimum possible level of sedation. Prominent earlier trials showed that patients whose sedation was routinely interrupted received less sedation overall, spent fewer days undergoing mechanical ventilation, and had a shorter stay in the ICU. In later related trials, daily interruption of sedation was associated with reduced administration of sedating mediations, reduced duration of mechanical ventilation, reduced length of stay in the ICU, and increased survival.

Sedating agents commonly used in the ICU are the benzodiazepines midazolam and lorazepam, the short-acting intravenous anesthetic agent propofol, and dexmedetomidine. Fentanyl and remifentanil are used for the combined analgesia and sedating properties they offer. The use of these agents has changed little in recent years of critical care practice.

The use of sedating agents is at least temporally associated with delirium. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* lists 4 domains of delirium: disturbance of consciousness, change in cognition, development over a short period, and fluctuation. Delirium is defined by the National Institutes of Health as a sudden severe confusion and rapid changes in brain function occurring with physical or mental illness. The most common feature of delirium is inattention. Delirium is a nonspecific, frequently reversible manifestation of acute illness that appears to have many causes including inadequate recovery from a sedated or oversedated state.

The pathophysiology of delirium associated with critical illness remains largely uncharacterized and may vary depending on the cause (see later). With many hypotheses and no definitive statements, pharmacologic management of delirium is largely empirical. Preliminary investigations with magnetic resonance imaging show an association between the duration of delirium in the ICU and cerebral atrophy with white matter disruption. Despite these preliminary data, there is no diagnostic blood, electrophysiological, or imaging test for delirium, which remains a clinical diagnosis. Estimates for the incidence of delirium in the ICU range from 20% to approximately 90% with the reported incidence affected by the characteristics of the population studied and the diagnostic criteria used. The identified risk factors include advanced age, coma at some point during the ICU stay, treatment with sedative medications, a neurologic diagnosis, and increased severity of illness. Some investigators have also associated the diagnosis of delirium with increased mortality and reduced long-term cognitive function.

There are 2 forms of delirium: hypoactive and agitated. When individual patients intermittently have both forms, it is termed mixed delirium. Hypoactive delirium is characterized by inattention, disordered thinking, and a decreased level of consciousness. This is the most common presentation for delirium in the critical care unit. Agitated delirium is much less common than hypoactive delirium. Patients with hypoactive delirium appear to be less likely to survive but have better long-term function if they survive than individuals with agitated or mixed delirium. Separating the effects of delirium from those of illness severity with respect to the risk of death is difficult because patients with more severe illness are at increased risk for both delirium and death. Thus, although a temporal association between delirium and worse outcome is clear, a causal relationship has not been established. A number of clinical scales have been identified to diagnose delirium. Unfortunately, the provider administering the scale may have a significant impact on the outcome. For example, research nurses identify delirium far less often than psychiatrists and neurologists. Thus, delirium frequently goes undiagnosed.

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There is some evidence that delirium can be prevented. Outside the ICU, reorientation, noise reduction, cognitive stimulation, vision and hearing aids, adequate hydration, and early mobilization reduce the incidence of delirium in hospitalized patients. The use of antipsychotic agents as prophylaxis, particularly haloperidol, has some proponents, but a large recent multicenter trial with a general ICU population failed to show a mortality benefit with haloperidol prophylaxis. Among other available studies, low-dose haloperidol and low-dose risperidone have been associated with a reduced incidence of delirium in patients undergoing elective surgical procedures. There are also some data to suggest that sedation with dexmedetomidine rather than benzodiazepines may reduce the incidence of delirium in the ICU.

When the presence of delirium is established, there are limited data to guide management. There are some data to support the use of the newer antipsychotic agent quetiapine in patients with delirium, but other studies using antipsychotic agents do not show particular benefit. There may be some benefit to the use of dexmedetomidine in patients with hyperactive delirium. Unfortunately, the science behind many of our interventions for this important problem is limited.

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Delirium is commonly screened by tools such as the Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). These clinical scoring systems are based on the evaluation of the level of consciousness and changes in cognition including fluctuation and acuteness. The use of these tools in clinical practice and research has increased rapidly in recent years, leading to a wide range of reported delirium incidence (see Reade and Finfer). Delirium has been associated with prolonged mechanical ventilation, ICU, and hospital stay and impairment of cognition. Other studies also link delirium to mortality.

Sedative and analgesic drugs are widely used in critically ill patients, but the interference of these agents with the assessment of delirium has not received wide attention. The effects of sedation on CAM-ICU and ICDSC were not considered in the validation of these clinical parameters and may not have been adequately considered in research performed with these instruments. Sedation alters level of consciousness, causes fluctuation of consciousness, and alters cognition. In some settings, light sedation alone may be enough to fulfill the features of delirium according to widely used clinical scores.

Studies using clinical evaluation of delirium with careful monitoring of sedation observed high delirium rates in patients who remained at light to moderate sedation levels despite the interruption of agent administration. The likelihood of delirium based on clinical parameters was reduced dramatically if assessments with persisting sedation despite sedation discontinuation were excluded. The incredible conclusion of this work is that persisting sedation effects may result in a diagnosis of delirium when commonly used screening tools are used.

Another study in medical patients critically examined the persistence of sedation effects and the diagnosis of delirium. Again, these authors found that sedation had a major influence on the relevance of delirium as indicated by a positive CAM-ICU assessment. Patients were over 10 times more likely to have a positive CAM-ICU score indicating delirium before stopping sedation as after stopping sedation. Patients with rapidly reversible sedation-related delirium in this work did not differ from patients with no delirium in any of the relevant patient-centered outcomes such as ventilator days, ICU length of stay, hospital length of stay, or hospital or 1-year mortality. In contrast, patients with persistent delirium after the discontinuation of sedation had more ventilator, ICU, and hospital days; were less likely to be discharged home; and were noted to have increased 1-year mortality. These results strongly suggest that the impact of sedation on the assessment of delirium should not be ignored. It may even be questioned whether rapidly reversible sedation-related delirium is delirium at all. Sedatives, analgesics, and anesthetics are readily capable of producing a state in which all the criteria of delirium screening tools may be temporarily fulfilled. In the critical care unit, long-term administration of sedatives may cause accumulation of the active drug and metabolites, especially with benzodiazepines and even usually short-acting drugs such as propofol, leading to prolonged sedation effects that may be diagnosed as delirium based on clinical parameters. Thus, it is fully conceivable that prolonged sedation may have direct toxic effects on the brain and contribute to complex brain dysfunction that screening tools identify as delirium.

A final report in this series of minority opinions reviews evidence for inflammation contributing to brain dysfunction and delirium in the critical care unit. Page et al observed that statin administration reduced the risk of a higher CAM-ICU score the following day. This association vanished when the authors controlled for C-reactive protein concentration. This study supports an evolving hypothesis of inflammation as one cause of brain dysfunction consistent with altered consciousness noted in early sepsis. The effects of sedatives superimposed on the effects of inflammation may increase the risk of brain dysfunction and create an impression of persistent delirium when clinical parameters for the assessment of this problem are used. It may be appropriate to combine sedation discontinuation with delirium screening and, if possible, prolong the sedation holiday until a steady awake state has been achieved and to report the actual sedation response during screening for delirium.

Of concern is the absence of the consideration of sedation effects reported with sedation use and sedation level during screening for delirium. If persisting sedation effects contributing to the diagnosis of delirium are present and sedatives readily produce such symptoms, the value of common clinical tools to identify delirium may be questioned in the absence of a biologic marker that confirms the impression created by clinical scores such as CAM-ICU or ICDSC.

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Delirium is a strong independent predictor of longer time on mechanical ventilation and in the ICU with increased