Review Article

Delirium prevention and management—less sedation and keep moving!

Bruno Gonçalves[1], Daniel Ferreira de Barros[1,2,3], Cássia Righy[1,4]

[1]Instituto Estadual do Cérebro, Rio de Janeiro, Brazil; [2]Hospital Norte D'Or, Rio de Janeiro, Brazil; [3]Hospital Quinta D'Or, Rio de Janeiro, Brazil; [4]Instituto Nacional de Infectologia, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

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Correspondence to: Cassia Righy, MD, PhD. Instituto Estadual do Cérebro, Rio de Janeiro, Brazil; Instituto Nacional de Infectologia, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil. Email: cassiarighy@gmail.com.

Abstract: Delirium is a highly prevalent syndrome in critical care patients, and its impact on patients' outcome is becoming increasingly recognized. Delirium is defined by the DSM-5 as an acute disorder of attention and consciousness, occurring in up to 80% of hospitalized patients in intensive care and is a predictor of several adverse events. There are many pathophysiological mechanisms implicated in the development of delirium ranging from alterations in neurotransmitter balance to brain inflammation. Delirium is a direct consequence of a medical condition, and may be induced by acute organ dysfunction or disease, so prompt treatment of the underlying condition is needed to reduce the incidence, severity, and duration of delirium. Though with a low level of evidence, administration of antipsychotic medications is recommended by various international guidelines and is the most used drug class to treat delirium. Prevention, with great emphasis on non-pharmacological measures, and recognition strategies are of utmost importance to deliver proper treatment and avoid worse outcomes in this group.

Keywords: Delirium; intensive care unit; dexmedetomidine; sedation

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Introduction

Delirium is a highly prevalent syndrome in critical care patients, and its impact on patients' outcome is becoming increasingly recognized. Delirium is defined by the DSM-5 as an acute disorder of attention, and fluctuating character of consciousness that is not explained by pre-existing neurological disease and that does not occur in the context of an essential reduction of awakening, as in coma. Using standardized assessment scores, delirium occurs in up to 80% of hospitalized patients in intensive care (1) and is a predictor of several adverse events, such as increased time in ICU and hospital, higher morbidity, higher risk of institutionalization, and mortality both in hospital and one year after discharge (2). In specific populations, such as patients with malignant neoplasms hospitalized in intensive care, our data show an incidence of acute cerebral dysfunction of 95% and its association with higher in-hospital mortality (3). Also, the occurrence of delirium is associated with the development of cognitive deficit in sepsis survivors after discharge (4).

A comprehensive meta-analysis by Zhang *et al.* (5) suggests that delirium has a high impact not only on mortality [odds ratio (OR): 3.22; 95% CI: 2.30–4.52], but also on complications during the course of ICU stay. Pooled together, acute respiratory distress syndrome, nosocomial pneumonia, cardiopulmonary edema, reintubation, self-extubation, removal of catheter, and cardiac arrhythmia, had an OR: 6.5; 95% CI: 2.7–15.6 on delirium patients against those without delirium. Both ICU length of stay was

higher when delirium was present, with a weighted mean difference (WMD) of 7.32 days (95% CI: 4.63–10.01 days) and duration of mechanical ventilation, with 7.22 more days (95% CI: 5.15–9.29 days) on patients with delirium. Throughout the studies included in this particular meta-analysis, the mean or median age ranged from 50 to 76 years, which means the results are not restricted only to older patients.

Pathophysiology

The brain has previously been described as an immune-privileged organ (6), inaccessible to deleterious systemic influences due to the presence of the blood-brain barrier (BBB). However, this concept has recently been challenged, with the knowledge that systemic inflammation influences brain function (7,8). Our behavioral responses to uncomplicated infections (sickness behavior) demonstrate that inflammatory mediators may signal to the brain to evoke significant changes in our behavior and metabolism (7). Most of the time, these changes are adaptive: they aim to rearrange essential priorities and preserve the energy of the body to be able to compose a febrile reaction and fight infection while suppressing the motor and social activity and isolate the individual from the rest of the community (8). However, there is considerable evidence to suggest that systemic inflammation may have deleterious effects on the brain if the inflammation is severe enough, or if the brain has vulnerabilities due to genetic predisposition, aging or neurodegenerative disease (9).

In addition to "sickness behavior", the other presentations of acute cerebral involvement in sepsis are delirium and coma. There are many pathophysiological mechanisms implicated in the development of delirium ranging from alterations in neurotransmitter balance to brain inflammation (10). For example, Hshieh *et al.* (11) suggest that the cholinergic system is strongly implicated in the generation of delirium, with reduction of the production and transmission of acetylcholine, since these processes are susceptible to hypoglycemia and oxidative stress.

Impact on the prognosis

Classical studies of the last two decades have managed to establish the relationship between the occurrence of delirium and worse medium and long-term outcome. Ely *et al.* (1), in his landmark paper, described that delirium was an independent predictor of 6-month mortality, and helped to raise awareness to the long-term consequences of delirium. Milbrandt *et al.* (12) found a relationship between increased hospital costs and the development of delirium in patients undergoing mechanical ventilation. In 2009, Pisani *et al.* (13) described that, in elderly patients admitted to the ICU, the duration of delirium was associated with a higher mortality rate in 1 year after hospital discharge. In 2010, Shehabi *et al.* (14) described that the duration of delirium was an independent predictor of death, mechanical ventilation and ICU length of stay.

In addition to increased mortality and hospitalization time, it is increasingly recognized that the occurrence and duration of delirium are associated with a reduction of long-term cognitive function, generating a public health problem among those who survive critical care. The myriad of symptoms after critical care discharge is called post intensive care syndrome (PICS) (4).

PICS is new or worsening impairments in physical, cognitive, or mental health status arising from critical illness and persisting beyond acute care hospitalization. The term could be applied to a survivor (PICS) or family member (PICS-F) (15). The manifestations of PICS include physical impairments, cognitive impairments (e.g., impaired executive function, memory, attention, and mental processing speed), and mental health morbidities that include acute stress disorder, anxiety, depression, and post-traumatic stress disorder (16). Preiser *et al.* (17) suggest that type 2 diabetes mellitus can be acquired during a stay in an intensive care unit [ICU-acquired diabetes (ICU-AD)] as an additional component of PICS because of insulin resistance due to stress hyperglycemia.

Management of delirium

Delirium is a direct consequence of a medical condition and may be induced by acute organ dysfunction or disease. Therefore, prompt treatment of the underlying condition is needed to reduce the incidence, severity, and duration of delirium. Besides acute disease, iatrogenic factors also may contribute to the development of delirium in ICU patients, either through the use of sedatives such as benzodiazepines, or related to the environment, such as physical restraints, confinement, and prolonged immobilization (18). Thus, these patients should be evaluated for identifiable and avoidable risk factors, to prevent delirium.

Treatment of delirium, once diagnosed, relies on medications to reduce its severity and duration. Though with low level of evidence, administration of antipsychotic

medications is recommended by various international guidelines and is the most used drug class to treat delirium (18). A systematic review on antipsychotics for the treatment of delirium did not show different efficacy between haloperidol, olanzapine, and risperidone in the management of delirium, and high dose haloperidol (in this setting defined as higher than 4.5 mg/day) was associated with a higher incidence of side effects (19). In a small randomized, double-blind, placebo-controlled study, 36 ICU patients were randomized to either quetiapine or placebo, combined with as-needed haloperidol. Quetiapine was associated with faster resolution of delirium, less agitation and higher rate of hospital discharge, but also with a higher rate of somnolence. Mortality and ICU length of stay were similar between the groups (20). Rivastigmine (a cholinesterase inhibitor) was tested for treatment of delirium in a multicenter, double-blind, placebo-controlled randomized trial, but was halted underway due to higher mortality in the rivastigmine group (21). Also, in another randomized trial comparing patients sedated with either midazolam or dexmedetomidine, a higher prevalence of delirium was found in patients who received midazolam (76.6% *vs.* 54%) (22). Another trial, comparing sedation with either lorazepam or dexmedetomidine found that dexmedetomidine was associated with more days free of delirium (7 *vs.* 3 days, on the lorazepam group) (23). However, the results of these trials are not enough to determine if that effect is due to benzodiazepines being a risk factor for delirium development or if dexmedetomidine actually has a protective action against delirium.

Despite being associated with increased mortality, it is unclear whether interventions aimed to treat delirium actually have an impact on short-term survival. In 2014, a systematic review of seventeen trials failed to show that interventions done in the ICU to reduce the duration of delirium would also change short-term mortality (24).

In light of sparse data on delirium treatment, the most recent international guidelines by Society of Critical Care Medicine (SCCM) (18) suggests that antipsychotics may reduce the duration of delirium, and does not recommend rivastigmine to reduce the duration of delirium in ICU patients. Also, it does not suggest using antipsychotics in patients at risk for torsades de pointes and suggests that in patients with delirium not related to alcohol or benzodiazepine withdrawal, dexmedetomidine rather than benzodiazepine should be used for sedation to reduce the development of delirium.

Prevention of delirium

Delirium prevention strategies can be divided in nonpharmacologic (e.g., early mobilization), pharmacologic, and combined approaches. Intensive monitoring of critically ill patients for delirium and early recognition is critical, as it can lead to earlier treatment and may improve patient outcomes (18).

Many risk factors are known to play a role in the incidence of delirium, such as dementia, older age, co-morbid illness, severity of medical illness, infection, "high-risk" medication use, diminished activities of daily living, immobility, sensory impairment, urinary catheterization, urea and electrolyte imbalance and malnutrition, and also mechanical ventilation. In order to improve outcomes, an important strategy is to consider and act on the modifiable risk factors, with a systematic evaluation, for instance, to reduce the use of invasive devices, removing them as soon as possible, and to promote cautious use of sedation (benzodiazepines), as both are known risk factors for the development of delirium (25,26).

Non-pharmacological strategies

Early mobilization was initially studied to improve functional outcomes in critically ill patients (18). In a randomized controlled trial published in 2009 (27), early exercise and mobilization were associated with better functional outcomes, shorter duration of delirium and more ventilator-free days. More recently, a retrospective study also evaluated early mobility protocols. The intervention group had fewer delirium days, lower hospital costs, improved functional outcomes, and fewer ventilator-associated events and pressure ulcers, with no more significant number of adverse events (28). In another prospective and observational study, the number of hours each patient was mobilized per day, along with access to television/radio, and the use of opioids were all factors associated with less delirium in critically ill trauma patients, and physical restraints and sepsis increased its likelihood (29).

In an elegant meta-analysis by Zhang *et al.* (30), with 18 studies pooled, early mobilization had a positive influence on outcomes of patients undergoing mechanical ventilation such as ICU length of stay (median difference of –1.75, 95% CI: –2.70 to –0.79; P=0.0003) and duration of mechanical ventilation (MD =–1.64, 95% CI: –2.41 to –0.87; P<0.0001). There was no statistical difference in mortality. Therefore, this meta-analysis suggests that an

early mobilization protocol is feasible, safe (as it didn't increase mortality or had a negative impact on outcomes) and can improve hospital outcomes. Taken together, these studies suggest that early mobilization is safe, unlikely to harm ICU patients, and may reduce the incidence and duration of delirium, with many other benefits as well (18).

Sleep deprivation is a common problem in the ICU, and many ambient stressors within the unit may have a detrimental effect on patients' sleep (noise, light, physical stimulation due to procedures, medication or examination) (31). Many studies on the effects of sleep deprivation demonstrate that it can cause all the symptoms of delirium, and electrophysiological studies demonstrate a relationship between sleep and delirium—the latter occurring in patients with higher loss of rapid eye movement (REM) sleep. Alterations in neurotransmitters (mostly acetylcholine) are implicated in both sleep disturbances and delirium. A recent review of the literature on this matter showed that pharmacological sleep interventions to improve its quality seems to be associated with improved cognitive outcomes in the ICU, with a reduction both in the incidence (median reduction of 43% to 12%) and in the duration of delirium. However, these studies on sleep interventions have many confounders, such as the heterogeneity and quality of the data. Still, studies targeting sleep optimization in the ICU are promising, as well as other non-pharmacological approaches, such as the use of earplugs and reduction of bright light during nighttime (32).

In Poland, a trial of nonpharmacological intervention delivered by trained volunteers in 130 patients (65 in the intervention group) resulted in a beneficial effect such as the less frequent use of antipsychotic medications, and a trend towards lower mortality and shorter hospital length of stay. The interventions were aimed at specific risk factors, e.g., disorientation, psychological distress, immobility, dehydration, malnutrition, sensory deprivation and sleep problems. Despite not being tested in ICU patients, these results are promising (33).

In an open-label Australian feasibility trial (34), patients on mechanical ventilation were randomized to receive earplugs in addition to standard care. Earplugs were placed on admission to the ICU and also were offered between 10 p.m. and 6 a.m. for the first night after extubation on the ICU. Though it was not the main outcome of the study, the median sound abatement was 7 dB, which could provide more comfort and sleep quality to the patient in the ICU. In another randomized trial (35), not specific for ventilation patients, found that the use of earplugs was associated with a reduced risk of confusion [hazard ratio (HR), 0.47; 95% CI ,0.27–0.82], and better reported sleep perception due to noise reduction. More evidence is needed to define the effect of earplugs use (especially on patients undergoing mechanical ventilation), however, since they are a low cost, simple and feasible intervention, it may be a useful tool in the prevention of confusion or delirium through the noise-abatement provided and better sleep quality.

Many professional and scientific societies have acknowledged the importance of non-pharmacologic measures in the prevention of delirium. The SCCM has issued a recommendation to perform early mobilization whenever feasible and to optimize the environment for patients, controlling light and noise, decreasing of stimuli at night, and, if possible, bundling care activities together (18).

The Italian consensus on delirium in older persons (36) also endorses its prompt recognition, with great detail to the nonpharmacological aspects of care: time and space reorientation, minimizing environmental changes, early mobilization, promoting sleep, maintaining adequate nutrition and hydration, visual and hearing aids (if used) and minimizing invasive measures (e.g., nasogastric tube).

It must also be noted that the caregiver shall be adequately trained on the importance of delirium recognition and management, without considering the patient or the protocols involved to be a nuisance (36).

Pharmacological strategies

There is not enough evidence to support a pharmacological strategy to prevent delirium. Effective pharmacological interventions to prevent delirium have not been identified in clinical studies thus far.

A small multicenter randomized, placebo-controlled trial with haloperidol or ziprasidone for delirium prevention in the ICU did not show any benefit from the treatment in either free days of delirium, mortality, ICU length of stay or ventilator-free days in both treatment and placebo groups (37). Another randomized, placebo-controlled trial evaluated the use of haloperidol in elderly patients admitted to the ICU after non-cardiac surgery, aiming to reduce the incidence of delirium. Though it did show benefit (incidence of delirium of 15.3% in the intervention group and 23.2% in the control group), most of these patients were not severely ill or under mechanical ventilation (38).

One randomized study evaluated dexmedetomidine versus morphine plus propofol after cardiac surgery.

Dexmedetomidine did reduce the duration of delirium (2 *vs.* 5 days), but not its incidence (39). Recently, another randomized and placebo-controlled trial in elderly patients, tested if dexmedetomidine use during non-cardiac surgery (and in the first two hours after the procedure) could be useful for delirium prevention. There was no difference between the two groups in postoperative delirium incidence (40). Another study tested ketamine in both major cardiac and non-cardiac surgery and showed no difference in postoperative delirium as well; however, the ketamine group had more hallucinations and nightmares than the placebo group (41). In a recent small Japanese placebo-controlled randomized trial, suvorexant (a selective orexin receptor antagonist, used for treatment of insomnia) was used as a strategy to prevent delirium in ICU patients, with promising results (0% *vs.* 17% of delirium development in the control group). However, further studies with a more substantial number of patients and more prolonged period of follow-up are still necessary to determine the benefits of this drug (42).

There are no high-quality studies that demonstrate a benefit of prophylactic delirium medications to the general ICU population. Further research is needed to better define the safety and efficacy of pharmacological delirium prevention in ICU patients (18).

The SCCM (18) addresses this matter by providing no recommendation for the use of dexmedetomidine to prevent delirium in ICU patients and do not suggest either haloperidol or atypical antipsychotics to achieve this goal.

Possibly a reasonable strategy is an ICU protocol combining routine pain and sedation assessments, along with delirium monitoring and prevention. Not only does it make it easier to follow an objective (e.g., daily interruption of sedation), but also facilitate communication between members of the multidisciplinary intensive care team, assessing the effectiveness of the strategies (18). One study evaluated a unit before and after the introduction of a protocol to monitor pain, agitation, and delirium. After the protocol implementation, patients received fewer opiates, had better analgesia management, shorter duration of mechanical ventilation, and a significant reduction in subsyndromal delirium. Delirium rates were similar. Mortality was also lower in the post-protocol cohort (43). Thus, delirium prevention is a multidisciplinary approach, with a multifactorial strategy, involving lesser use of sedation and benzodiazepines, goal-oriented sedation, early mobilization, improvement of sleep quality in the ICU and reorientation and other non-pharmacological interventions with particular attention to the possibility of iatrogenic effects.

Conclusions

Delirium is an important syndrome, often under-recognized or under-valuated, with many clinical repercussions on the outcome of critically ill patients. Prevention, with great value in non-pharmacological measures, and recognition strategies are of utmost importance to deliver proper treatment and avoid worse outcomes in this group.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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