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## Prevention of delirium in critically ill patients: a new beginning?

*Prevenção do delirium em pacientes críticos: um recomeço?*

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Delirium is a severe confusional state that represents an acute brain dysfunction encompassing a wide array of clinical manifestations.<sup>(1)</sup> Substantial evidence demonstrates that delirium is associated with worse outcomes for critically ill patients, including increased duration of mechanical ventilation, length of hospital stay, cost and mortality.<sup>(2,3)</sup> Furthermore, despite advances in life support, critically ill patients that present with delirium during an intensive care unit (ICU) stay may experience impaired global functional recovery and long-term neurocognitive sequelae.<sup>(4)</sup> Therefore, several studies have been performed to test the effects of preventive pharmacologic interventions<sup>(5)</sup> on the incidence and/or duration of brain dysfunction, but the majority of these therapies remain unproven. These interventions have involved altering sedation paradigms by reducing use of benzodiazepines, the administration of typical and atypical antipsychotics, and the use of cholinergic agents such as rivastigmine.

Statins are candidate drugs hypothesized to both prevent and treat delirium via anti-inflammatory effects that may modulate the molecular pathways of inflammation and microglial activation, which are key pathways in the pathogenesis of delirium.<sup>(6)</sup> In this issue of *Revista Brasileira de Terapia Intensiva*, Cruz et al.<sup>(7)</sup> tested the hypothesis that patients who received preoperative statins would have a lower incidence of delirium after cardiac surgery. A total of 169 patients were enrolled, and information regarding patient demographics, statin exposure, and outcomes including the occurrence of delirium was evaluated. The authors reported no significant differences in either the demographics or the occurrence of delirium between the statin users and non-users. This study has an interesting rationale based both on the pathophysiologic aspects and the target population but has significant limitations that preclude any inferences regarding the role of statin medications in delirium prophylaxis. First, the limited sample size and the relatively low number of patients that developed delirium (n=23) prevented in-depth analysis, and the use of a different methodology may have led to substantially different conclusions. The use of multivariable analysis and propensity scores are examples of methods that are increasingly applied in the critical care literature as ways to both identify factors that are independently associated with outcomes and adjust for potentially confounding factors. Second, as in any observational study, the authors were not able to control the doses, durations and indications of the statins. Such variability may

**Conflicts of interest:** None.

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lead to so-called “healthy user effects” and other indication biases. Finally, the continuation of statins after surgery was not evaluated in detail.

The results of this study and the conflicting reports of Redelmeier et al. and Katznelson et al.<sup>(8,9)</sup> should by no means dampen our enthusiasm for studying the role of statin medications as a preventive or treatment modality for delirium given the pleiotropic properties of statin medications and the limitations of these prior although important studies. Both in vitro and human studies have shown that in addition to their effect on cholesterol synthesis, statins have anti-inflammatory, immunomodulatory, endothelial function-enhancing, and anticoagulant effects.<sup>(10)</sup> These effects may prevent or attenuate delirium during critical illness by acting on causative mechanisms including neuroinflammation, blood-brain barrier injury, neuronal apoptosis, ischemia and hemorrhage, and microglial activation. Large observational studies are therefore warranted to first examine the role of statin medications given prior to and during critical illness in modulating delirium and perhaps even long-term cognitive impairment. Coupling the clinical outcomes with the measurement of inflammatory biomarkers and markers of endothelial injury and/or activation may provide further mechanistic information regarding the role of statins in reducing brain dysfunction and additional insights into the optimal duration and dosage of statin medications required to attenuate these markers of injury. If the results of observational studies are promising, randomized, placebo-controlled trials could investigate the efficacy of statin administration initiated early during an ICU stay for the prevention or treatment of delirium and its related neurocognitive sequelae. Particular attention must be paid to identifying and separately studying the role of statin administration in prior statin users and statin-naïve patients, especially given recent reports suggesting an increase in inflammation in statin users whose medications are withheld. Given the possibility of differential effects on neuroinflammation during critical illness, both lipophilic and hydrophilic statins should be tested in clinical trials. Adequate sample sizes for important subgroups such as the elderly, those with sepsis, and those with prior atherosclerotic disease should be considered. Finally, the safety profile of drugs administered during critical illness is always a concern due to alterations in kidney and liver function and other factors predisposing patients to adverse reactions; fortunately, statins are generally

safe, resulting in a very low incidence of myopathy (0.01%) and liver enzyme abnormalities (0.1%) at standard doses.

The question remains, however, regarding what should clinicians do until clinical trials provide answers with respect to the best pharmacological and non-pharmacological approaches for preventing and treating delirium. Although its pathophysiology is not fully understood, several studies have identified factors associated with increased risk of delirium.<sup>(11,12)</sup> Several factors such as age, comorbidities, dementia and genetic factors cannot be modified by medical intervention but provide the clinician with an assessment of the individual risk for each patient. In contrast, numerous risk factors for delirium are modifiable, and easy and inexpensive interventions are available, e.g., benzodiazepine-sparing sedation, early mobility, the correction of hydro-electrolytic disturbances, the avoidance of hypoxia, early liberation from mechanical ventilation and the removal of invasive devices (such as intravenous and urinary catheters). These interventions, although based on evidence showing reductions in the risk of delirium, are far from being widely implemented in intensive care units in Brazil<sup>(13)</sup> or worldwide.<sup>(14)</sup> As an interesting and practical approach to this issue, the concept of “liberation and animation” has been proposed. The pillars of this approach involve keeping ICU patients comfortable and free from pain but as awake as possible to employ strategies to liberate critically ill patients from mechanical ventilation early on and to engage them in physical and occupational therapy<sup>(15)</sup>. One such organizational framework to help liberate and animate patients is the ABCDE bundle, which consists of Awakening and Breathing coordination regarding daily sedation and ventilator removal trials, Choice of analgesic and sedatives as needed, Delirium monitoring and management, and Early mobility and exercise. Elements of this ABCDE bundle have been shown to be associated with a shorter duration of mechanical ventilation, a reduced length of ICU stays, decreased duration and incidence of delirium, decreased cognitive impairment and even improved survival. With the validation of easy-to-use bedside delirium monitoring instruments, a full adherence to care measures and trends in the process of delirium intervention should be introduced in the ICU, and these measures can be used as quality indicators. We believe that delirium is a major patient safety issue, and reducing the incidence of delirium should be targeted in the ICU environment.

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