

The impact of sedation protocols on outcomes in critical illness

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Critically ill patients often require pharmacologic sedation to treat pain, agitation, and delirium or to tolerate mechanical ventilation and invasive procedures (1). Over the last several decades, our understanding of medications commonly administered for sedation in the critically ill has increased and we now appreciate both the short and long-term consequences of prolonged exposure to these agents. In fact, the Society of Critical Care Medicine recently revised its sedation guidelines based on emerging evidence that certain sedation practices may influence outcomes in critical illness (2). For example, it has become quite clear that prolonged exposure to benzodiazepines and, to a lesser extent opiates, contributes to the development of delirium, while the use of dexmedetomidine might decrease the risk. However, it would be premature to suggest that we currently know enough to protocolize “optimal” sedation algorithms. Despite this recent interest in dexmedetomidine as a “delirium sparing” sedative-hypnotic, a recent meta-analysis concluded that no definitive conclusions on the use of dexmedetomidine can be drawn yet and more clinical trials seem warranted (3). In any case, delirium is associated with increased mortality, prolonged stay on the intensive care unit (ICU) and the development of post ICU cognitive impairment, and the search for new strategies to prevent or treat delirium is currently an area of intense investigation (4).

Several studies suggest that the use of dexmedetomidine or propofol, rather than a benzodiazepine, to sedate critically ill patients may reduce length of stay in ICUs or the duration of mechanical ventilation. In a large retrospective study, Klompas *et al.* found that dexmedetomidine was associated with shorter time to extubation than propofol (1). However, whether or not this difference is clinically relevant (aside from cost), or more specifically whether this difference is associated with either

short-term or long-term mortality, remains unclear.

Interestingly, while dexmedetomidine reduces the duration of mechanical ventilation compared with midazolam or propofol, an increase in adverse effects has also been observed with dexmedetomidine sedation regimens (5). Bradycardia and hypotension are well-described side-effects of dexmedetomidine and in clinical practice appear to be observed relatively frequently during dexmedetomidine sedation. In addition, dexmedetomidine might not be suitable as a single agent for deep sedation. Nevertheless, numerous outcome studies focusing on sedation algorithms in critically ill patients clearly find that protocolized sedation pathways, utilizing standardized, validated patient assessment tools, can reduce ventilator days, ventilator-associated pneumonias, and delirium and hospital length of stay (5-9). It is important to note that many of these pathways include ‘wake up and breathe’ protocols that are not focused only on sedation agents, but also on a strict schedule of daily sedation interruption (10).

Based on this accumulated evidence that sedation protocols reduce the incidence of several adverse outcomes, it is quite surprising that information on long-term mortality is scarce. Studies that have explicitly evaluated long-term mortality have not found significant differences in mortality between different sedation and weaning protocols (1,11). A possible explanation might be the multifactorial nature of “critical illness”, which can be caused by so many different factors, including hospitalization, dementia, delirium, pain, sedation, polypharmacy, organ dysfunction, metabolic and electrolyte disturbances, brain injury, trauma, oxidative stress, hypoxemia, ischemia, or infection (4). Moreover, while we seem to understand the influence of sedatives on the development of delirium or the duration of mechanical ventilation, essentially nothing is known about

the molecular mechanisms underlying these phenomena. Confronted with this void, it seems clear that basic science research has a crucial role to play in this important aspect of intensive care medicine.

While there have been few mechanistic studies in critical illness, it is known that critically ill patients, and in particular patients diagnosed with sepsis, have a very distinct metabolic phenotype (12). In particular, mitochondrial dysfunction, endothelial disruption and derangements of NO synthesis have been all found to be associated with critical illness. Recent studies have now linked these defects with dysfunctional expression of circadian rhythm proteins (13-15). Indeed, a very common and significant feature of critical illness is a severe disruption of circadian rhythms with altered sleep-wake cycles and cognitive dysfunction (16). Moreover, medications used in the care of critically ill patients such as benzodiazepines, which have been implicated in the pathogenesis of delirium and prolonged mechanical ventilation, might also be the drugs responsible for disrupting circadian rhythms in those patients (13,14,17). Melatonin, secreted in a circadian manner by the pineal gland, is a well-established marker of a functional circadian rhythm. It is not surprising, then, that critically ill patients not only have altered sleep patterns but also abnormal melatonin levels. Recent studies of melatonin expression have therefore generated an interest in the use of exogenous melatonin and melatonin agonists to improve sleep and cognitive function in critical illness. Indeed, a promising randomized controlled trial demonstrated effectiveness in the use of a melatonin agonist (Ramelteon) versus placebo in the prevention of delirium. In the context of a possible melatonin-circadian rhythm-clinical disease axis, studies on endogenous and exogenous melatonin, pharmacological agonists, and associated genetics could provide important insight into the development and treatment of critical illness (13). Interestingly, a recent trial found that long term enteral melatonin supplementation may result in a decreased need for sedation, with improved neurological parameters and cost reduction (18). Similarly, another study on weaning from mechanical ventilation found that delirium is frequent at the initiation of ventilator weaning and is associated with a prolongation of weaning and an alteration in the circadian rhythm of melatonin excretion (19). However, it remains to be seen if melatonin agonists will be circadian disruption's silver bullet. In fact, we have to fully understand the impact of many common clinical scenarios on circadian rhythms, including severe illness, stress, noise, surgery, sepsis, drugs,

nighttime exposure to artificial lighting and much more. It hardly needs to be pointed out that a single therapy might not be sufficient to restore disrupted circadian rhythms in critically ill patients. More likely, implementation of a circadian "care bundle", (for example, a combination of melatonin agonists, targeted daylight exposure in the ICU during daytime hours, and reduced exposure to noise and artificial light during the night) together with optimized sedation and weaning protocols, will offer the best hope of restoring disrupted circadian rhythms, and eventually might improve mortality in critical illness (14).

While we will have to wait for clinical trials testing such a multimodal therapeutic approach, there is little doubt that circadian rhythms have important impacts on human health and disease. Recent evidence suggests that disrupted circadian rhythms increase the risk of many common diseases, including myocardial infarction, stroke and sepsis (14). Moreover, the two-hundred most commonly prescribed medications in the United States have at least some circadian aspect to their pharmacology (20). In fact, chronotherapy, the administration of medication at very distinct time points during the day, is a well-established approach in a few areas, but not established in everyday clinical practice, including pharmacotherapy in critical illness. Future studies in critically ill patients should begin to record the time points when certain interventions are performed for analysis of circadian effects. In addition, continuous drug infusions or feeding strategies will need to be critically evaluated in future ICU studies.

In summary, sedation and weaning guidelines seem to improve outcome parameters in critically ill patients, but overall mortality reduction has yet to be convincingly demonstrated. Based on the complex, multifactorial origins of critical illness, a multimodal therapeutic strategy seems more likely to be effective. Future research will need to consider the influence of circadian rhythms on both critical illness and ICU sedation if we ever hope to find "optimal" sedation strategies.

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Footnote

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