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DURATION OF DELIRIUM AND PATIENT-CENTERED OUTCOMES: EMBRACING THE SHORT- AND LONG-TERM PERSPECTIVE

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Delirium has been described in medical writings as early as the first century (1), yet it remains a challenge for modern-day physicians and its pathophysiology remains poorly understood. The concept resonates within the critical care community because it is common in the critically ill (2-4) and because delirium is associated with increased short- and long-term mortality (2-4). Moreover, delirium has been associated with long-term cognitive and functional impairment in survivors of critical illness (5-8). From a patient and family centered care perspective, its development matters deeply to the loved ones at the bedside, as eloquently detailed in a recent account of one family's frightening encounter with delirium (9). Delirium undermines our rational self, it challenges the Cartesian principle “Cogito ergo sum” (I Think, Therefore I am), and in its wake, it leaves the patient and their family vulnerable and potentially, forever changed (5-10).

To combat the deleterious consequences of delirium, intense efforts have been directed at reducing the duration of delirium. A critical question, addressed in this issue of the journal by Al-Qadheeb and colleagues, is whether the myriad treatments that have been evaluated to reduce the duration of delirium have an effect on short-term mortality (11). Through a rigorous systematic search, the authors identified 17 randomized trials conducted between 2001-2012 that enrolled 2,849 subjects. The trials examined the effects of pharmacologic and non-pharmacologic interventions hypothesized to reduce the duration of delirium. The trials enrolled diverse populations at varying stages of delirium. Similarly, the methodology for delirium assessment varied in terms of frequency, personnel performing the assessment, and the assessment tool used.

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Using a random effects model meta-regression, Al-Qadheeb et al. found that delirium duration was significantly reduced by the interventions, although the effect size was modest (0.64 days less, $p=0.01$) and significant heterogeneity ($p<0.001$) existed across studies. In the 13 trials that reported short-term mortality, there was no significant survival difference between the intervention and control groups (15.6% vs. 16.5%, $p=0.54$). Consistent with the direct comparison, the meta-regression analyses demonstrated that delirium duration was not associated with a reduction in short-term mortality (slope of the $\ln(\text{RR mortality}) = -0.17$; 95% CI -0.39 to 0.04; $p = 0.11$), nor was the relationship substantially different in the extensive sensitivity analyses conducted.

The strengths of the present study are numerous. First, the authors have tackled an important, and challenging, question in critical care medicine. Second, the methodology employed was rigorous and comprehensive, beginning with their extensive literature search and carefully selected eligibility criteria, and as demonstrated in their systematic data abstraction and bias assessment. Third, after their attempt to use a random effects model meta-analysis was thwarted, they expertly utilized a random effects model meta-regression to answer the questions at hand. Further, their use of multiple sensitivity analyses provide the reader with an additional level of confidence that the results were not due to an analytical decision.

Several potential limitations of the study should be noted. First, the 17 trials included a heterogeneous group of pharmacologic (antipsychotics, alpha-2 receptor agonists, and acetylcholinesterase inhibitors) and mixed/non-pharmacologic (daily sedative interruption, early mobilization, and protocolized peri-operative perfusion pressure) interventions. The studies enrolled medical and surgical ICU patients, with varied severity of illness. While interventions that benefit a broad group of patients would be generalizable, delirium varies by patient population, the underlying illness, and sedation practice. As such, the heterogeneity observed, while appealing in some ways, makes interpretation of the results challenging. Second, because the relationship described by a meta-regression is an observational one, confounding is an important potential bias (12). Despite conducting a number of important subgroup analyses, the potential for residual confounding of observed (e.g., illness severity) and unobserved (e.g., duration of coma) covariates exists (13-14). Future studies exploring the relationship between delirium duration and its outcomes will need to account for variations in illness severity and sedation use over time, incorporate the complete spectrum of acute brain dysfunction given the independent association between coma and mortality (13-14), and assess the short- and long-term consequences of delirium. Last, given the number of trials included in the meta-analysis, it is plausible that the study was underpowered to detect whether interventions that reduce delirium duration result in short-term survival benefit.

Despite its potential limitations, there are two important findings in the present study by Al-Qadheeb and colleagues. First, a diverse group of pharmacologic and nonpharmacologic interventions do appear to reduce the duration of delirium. Second, interventions employed to reduce the duration of delirium may not result in a similar reduction in short-term mortality. Several interpretations exist to reconcile the present findings with a recent systematic review of observational studies that found that delirium was independently

associated with increased mortality (15). First, these findings may signal that interventions that reduce delirium do not actually impact short-term mortality. This explanation, which requires confirmation given pathophysiologic rationale (2) and prior observational studies (2-4), would suggest that the prior association, at least in the short-term, was not causal. Alternative explanations, which also require further investigation, include: the effect size seen across these heterogeneous studies was too small to see a mortality reduction, the means to reduce delirium and the method of delirium assessment are critical factors in the relationship which could not be adequately analyzed given the sample size and last, the ability to impact mortality may be mediated by delirium prevention to a significantly greater degree than reducing delirium duration once delirium has begun.

In summary, this rigorous systematic review and meta-regression leads us to conclude that heterogeneous “delirium-reducing interventions” across diverse patient populations can, in fact, reduce the duration of delirium. And yet, the achieved benefit in reducing the duration of delirium may not result in an effect on short-term mortality. While further research is required to confirm these findings, the opportunity to improve the lives of patients and their families, by reducing the incidence and duration of delirium experienced in the ICU with an eye on the short- and long-term perspective, remains a viable and important objective for our field and for those that we serve.

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