Intraoperative Glycemic Control to Prevent Delirium after Cardiac Surgery

Steering a Course between Scylla and Charybdis

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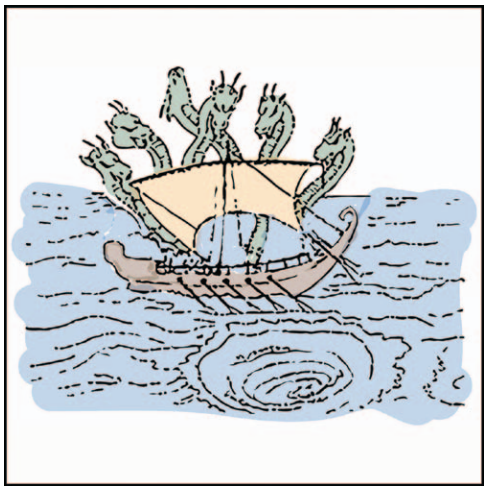
THE face of delirium is intuitively recognizable to most clinicians (at least in severe cases)—the wandering eyes, the lack of attention and focus, and the sense that a patient is "not all there." Delirium is a serious postoperative complication with long-term sequelae for patients and families, including persistent cognitive dysfunction,[1] increased hospital length of stay,[2] and increased mortality risk.[3] The recognition of these potentially devastating outcomes is reflected by the increasing number of articles published on this topic recently (fig. 1) and has led to an investigation by Saager *et al.*[4] in this issue of the effects of intraoperative tight glycemic control on the incidence and severity of postoperative delirium.



***"... avoiding even mild hypoglycemia may be equally as important as avoiding hyperglycemia when it comes to preventing postoperative delirium, just as avoiding the rocks of Scylla was equally as important as avoiding the whirlpool of Charybdis for sailors in Homer's* Odyssey."**

Despite the straightforward clinical presentation of delirium, its well-defined prognostic implications, and a large research focus, we still lack a clear understanding of what postoperative delirium is at a brain systems level, and also struggle with how to best diagnose delirium. These limitations are not surprising considering that delirium is a disorder of consciousness, and we lack a brain circuit level understanding of consciousness itself. The entire situation is reminiscent of the words of Voltaire who once remarked: "Doctors pour drugs of which they know little, to cure diseases of which they know less, into human beings of whom they know nothing."

To be fair, there is some evidence that delirium reflects alterations in specific neurotransmitters (reviewed in Inouye *et al.*[5]). But the brain is not simply a soup bowl of neurotransmitters. The 80+ billion neurons that make up the brain[6] are better conceptualized as a circuit board with 80+ billion nodes, each of which is connected to 10,000+ other nodes in the circuit. To say that delirium results from altered neurotransmitter levels is like saying that an error in the function of a computer program results from altered electricity levels inside the computer. Although true, neither statement is particularly informative. Neuroimaging and electroencephalography studies demonstrate that delirium is associated with disruption of cortical and subcortical functional connectivity,[7–9] but the extent of connectivity disruption necessary or sufficient to cause delirium is unknown.

According to the definition in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, inattention is a necessary component of delirium. However, inattention can be measured by a deficit in either simple attention or working memory. Simple attention can be measured by saying the letters SAVEAHAART aloud and instructing the patient to squeeze the tester's hand every time he or she hears the letter "A."[10] Working memory is a more complex cognitive function that requires patients to transiently hold and process information and can be measured by asking a patient to recite the months of the year backward. Working memory declines with age.[11] Thus, classifying patients as delirious if they cannot complete a working memory task risks mislabeling a presurgery working memory deficit as delirium. This is a potential problem if presurgery

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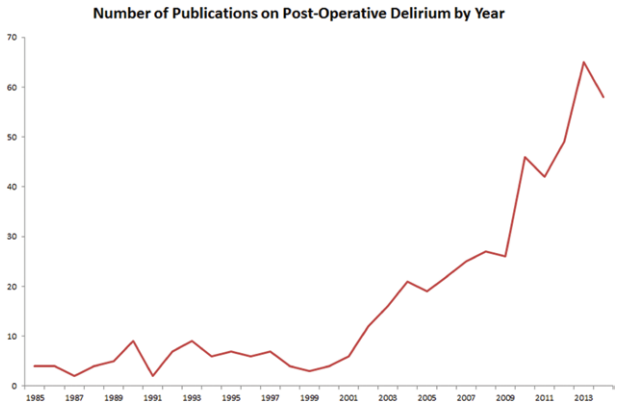

Fig. 1. This figure was made using Microsoft Excel (Microsoft Corporation, USA), with data obtained from performing a PubMed search using the terms "Postoperative Delirium" and each successive publication year from 1984 through 2014.

baseline cognitive assessments are unavailable, as in the study by Saager *et al.*

Other challenges to accurately diagnose delirium include the influence of practice effects on repeated delirium assessments[12] and the difficulty in quantifying the degree of "clinically meaningful" postsurgery cognitive change necessary for delirium.[13] Education level ("cognitive reserve") and varying cognitive effort on the part of patients may also affect the sensitivity of delirium detection.[14] These challenges may explain why studies have detected delirium rates after cardiac surgery ranging from more than 50%[15] to less than 15%[16] and argue strongly for a multidisciplinary approach to delirium detection, monitoring, and treatment.

Despite these challenges, the clear long-term sequelae of postoperative delirium mandate that we as physicians attempt to prevent it even if we do not fully understand what causes it or how best to measure it.[17] Recent attention has focused on inflammation as a contributor to postoperative delirium[18] and possibly to longer term cognitive dysfunction as well.[19,20] Hyperglycemia has also been identified as a possible contributor to adverse postoperative outcomes[21] and has been correlated with increased inflammation.[22] Conversely, insulin administration decreases inflammation.[23]

On the basis of these findings, Saager *et al.*[4] now report the results of a randomized double-blind trial that examined the effect of tight intraoperative glycemic control (*via* a hyperinsulinemic–normoglycemic clamp) *versus* standard glycemic control, on the incidence of postoperative delirium in patients undergoing cardiac surgery. Surprisingly, and contrary to the hypothesis of authors, patients in the tight glycemic control arm of the study had a higher incidence of delirium.

Are these results valid? Aside from insulin administration, intraoperative characteristics were generally similar among patients in both study arms (table 2 of Saager *et al.*[4]). Surgery duration, clamp time, and bypass time were all slightly longer in the tight glycemic control arm, although these differences were small relative to the differences in insulin administration. Thus, it is likely that the differences in delirium outcomes between the study arms are primarily due to the differences in insulin administration.

What do these results mean? This trial was based on the rationale that hyperglycemia has been associated with adverse events, although not with delirium itself *per se*,[21] and that insulin therapy has antiinflammatory effects that would decrease delirium incidence if delirium is caused by inflammation. However, even mild hypoglycemia is associated with alterations in cognitive performance,[24] and brain function and connectivity.[24–26] Indeed, hypoglycemic episodes in patients with type II diabetes even predict the development of dementia.[27] Consistent with this literature, Saager *et al.*[4] report a trend toward *increased* delirium rates with each 10 mg/dl decrease in glucose levels. This finding barely missed statistical significance ($P = 0.06$), likely due to insufficient power (a type II error). Thus, one interpretation of the study results is that the increased incidence of mild hypoglycemia in the tight glycemic control arm adversely affected neurocognitive function and led to postoperative delirium.

Where do we go from here? The results of this trial fit nicely with other studies showing that tight glycemic control is associated with increased adverse event rates compared with standard glycemic control[28] and suggest that providers should consider avoiding tight glycemic control in cardiac surgery. Saager *et al.*[4] should be praised for the extraordinary effort that went into carrying out this study on the effect of tight intraoperative glycemic control on postoperative complications including delirium. Overall, the results suggest that avoiding even mild hypoglycemia may be equally as important as avoiding hyperglycemia when it comes to preventing postoperative delirium, just as avoiding the rocks of Scylla was equally as important as avoiding the whirlpool of Charybdis for sailors in Homer's *Odyssey.*

This article also raises several questions for future inquiry: Would tight glycemic control be more beneficial during the postoperative period than during surgery itself? This issue is relevant because mild hypothermia increases insulin resistance,[29] and thus, mild hypothermia during cardiopulmonary bypass may also attenuate the antiinflammatory effects of insulin. More broadly, these results suggest that improving our understanding of what delirium is at a brain systems level and from a neuropsychological perspective may allow us to design interventions that will have a high likelihood of preventing delirium and its long-term sequelae.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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