

## Targeted Prophylaxis of Postoperative Delirium

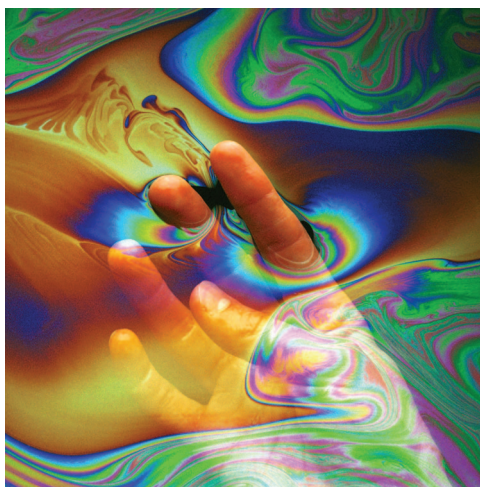


This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

**I**N this issue of ANESTHESIOLOGY, Hakim *et al.* present results of a randomized trial of a pharmacologic intervention to prevent development of postoperative delirium in patients who demonstrated early signs of cognitive instability.<sup>1</sup> Delirium is a serious and frequent postoperative complication that is frightening for patients and stressful for families. Delirium is associated with prolonged critical care and hospitalization, long-term cognitive decline, and mortality.<sup>2–4</sup> The syndrome is most common in geriatric surgical patients (15–62%)<sup>5,6</sup> and is especially common among patients requiring intensive care (70–87%).<sup>5,6</sup>

Previous studies indicate that prophylactic administration of antipsychotic medications reduces the risk of developing postoperative delirium,<sup>7</sup> although a clear effect on the consequences of delirium remains to be established. Given that many surgical patients do not develop postoperative delirium, it is inefficient to treat all with drugs that incur some cost and are at least potentially associated with complications. Even among higher-risk populations, it would thus be helpful to target prophylaxis toward patients most likely to become delirious.

Hakim *et al.* approach this issue by restricting prophylaxis to patients who had some evidence of disturbed cognition but who did not (yet) meet the formal criteria for a delirium diagnosis. Specifically, they defined “subsyndromal” delirium by a score of 1–3 (of a maximum of 8) on the Intensive Care Delirium Screening Checklist scale.<sup>1</sup> This well-vali-



***“... targeted prophylaxis [for delirium] substantially reduces the number of patients requiring drug administration.”***

dated scoring system is an alternative to the widely used Confusion Assessment Method for critical care patients (CAM-ICU). There is currently no consensus on the definition of subsyndromal delirium, but a score of 1–3 on the Intensive Care Delirium Screening Checklist scale has been used previously, and has been associated with worsened outcome.<sup>8,9</sup>

Their approach proved effective. Among 177 patients meeting enrollment criteria (including not already being delirious), 76 never developed subsyndromal delirium and thus avoided prophylactic treatment. In addition, of 51 subsyndromal patients given prophylactic risperidone (an atypical antipsychotic agent that appears to prevent delirium), 7 (14%) developed delirium; in contrast, 17 of 50 patients (34%) given placebo developed delirium ( $P = 0.03$ ).

The efficacy of risperidone was thus almost exactly as reported previously by Prakanrattana and Prapairakool in which a group of high-risk patients were randomized to risperidone or placebo without considering subsyndromal status: 32% *versus* 11%,  $P = 0.01$ .<sup>7</sup> Two studies thus document the efficacy of risperidone for prevention of delirium. But Hakim *et al.* also show that—even within a high-risk population—treatment can be further targeted, thus preventing unnecessary drug administration to approximately 40% of the patients.

The overall delirium rate reported by Hakim *et al.* (24 cases among 177 patients) was only 13%. Even if the delir-

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◆ This Editorial View accompanies the following article: Hakim SM, Othman AI, Naoum DO: Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: A randomized trial. ANESTHESIOLOGY 2012; 116: 987–97.

ium rates were similar in the treatment and control groups (as if risperidone had not been given), the rate would be 19% (34 cases among 177 patients). This incidence is very much on the low end of previous reports for delirium in elderly patients recovering from cardiac surgery. However, clinicians are increasingly aware of delirium and many hospitals have implemented guideline recommendations including sedation holidays, promoting a natural sleep-wake cycle, and family education. Furthermore, the incidence reported by Hakim *et al.* is similar to that reported in more recent literature on delirium. It thus seems likely that the current incidence of delirium is considerably lower than initially reported.

The study of Hakim *et al.* was well designed and executed. For example, blinding was maintained all the way through data analysis, which reduces the risk of bias. But there are also some limitations readers might consider. For example, allocation was revealed once patients became delirious. (Unblinding could have been avoided because the rescue treatment in both cases was additional risperidone and, if necessary, haloperidol.) The primary endpoint was thus fully blinded; however, secondary outcomes were not, including critical care and hospital length-of-stay and severity and duration of delirium. None of these endpoints differed significantly, however. This result is consistent with previous work suggesting that antipsychotic agents reduce the fraction of patients who become delirious, but does not improve the course in patients with delirium.

Sample size for the study of Hakim *et al.* was based on local clinical experience, which suggested a delirium rate of 25% in untreated subsyndromal patients *versus* only 5% in patients given prophylactic risperidone. This anticipated factor-of-five treatment effect seems biologically implausible; furthermore, it is far greater than the factor-of-three effect reported by Prakanrattana and Prapaitrakool in the only previous study of prophylactic risperidone for prevention of delirium.<sup>7</sup> In fact, the benefit observed by Hakim *et al.* was similar at a factor of 2.5. Consequently, their study was marginally powered even for their main effect, and quite under-

powered for secondary outcomes. Small studies often overestimate true treatment effects; large trials evaluating the important strategy suggested by Hakim *et al.* are thus very much needed.

In summary, Hakim *et al.* confirm that risperidone is effective for preventing postoperative delirium. Importantly, they extend previous reports by showing that targeted prophylaxis substantially reduces the number of patients requiring drug administration.

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