The Cognitive Neuraxis: Epidurals and Postoperative Delirium

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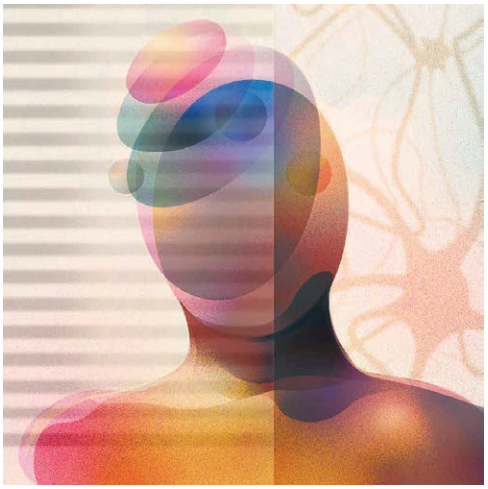
Delirium is a distressing syndrome that affects many surgical patients. Postoperative delirium is associated with falls, cognitive and functional decline, and prolonged hospitalization.[1] Indeed, delirium is a major public health issue, and postoperative delirium serves as a target for surgical quality improvement.[2] A promising strategy for reducing risk involves sustained interventions that simultaneously target multiple risk factors.[3] Epidural analgesia is one such candidate intervention that has been demonstrated to reduce key delirium risk factors: pain, opioid consumption, and inflammation.[4–6] Furthermore, epidural therapy can be continued over multiple days, particularly during time windows of peak delirium risk. Taken together, it seems plausible that such a sustained intervention, which simultaneously targets multiple risk factors, could reduce risk of postoperative delirium.



"Epidural analgesia is…[an] intervention that has been demonstrated to reduce key delirium risk factors: pain, opioid consumption, and inflammation."

As reported in this issue of Anesthesiology, Li *et al.* sought to determine whether combined general-epidural anesthesia, with continued postoperative epidural analgesia, would reduce the risk of postoperative delirium in older surgical patients.[7] To address this question, the authors conducted a multicenter, randomized controlled trial with more than 1,800 patients presenting for major thoracic or abdominal surgery. Patients were randomized to general anesthesia with intravenous analgesia or combined general-epidural anesthesia and continued postoperative epidural therapy, with epidural placement before induction of anesthesia. The findings revealed a significantly lower overall incidence of postoperative delirium in the epidural group (1.8%) compared to those randomized to general anesthesia (5%). This risk reduction was similar in the intention-to-treat analysis (*i.e.*, analysis based on initial group allocation) and the per-protocol analysis, which excluded participants with key protocol deviations such as failed epidural or group crossover. Within the first week after surgery, patients randomized to an epidural had an approximately 65% risk reduction of developing delirium at any given time compared to the control group. Participants in the epidural group also experienced less moderate-to-severe pain, oral and intravenous opioid consumption, and postoperative nausea and vomiting. In terms of undesired outcomes, intraoperative hypotension and vasopressor use were more common in the epidural group. Overall, these findings in the routine surgical setting suggest that epidural use reduces the risk of delirium and improves early postoperative pain management.

It is conceivable that epidural analgesia could alleviate delirium risk. Pain impairs cognitive flexibility,[8] and epidural therapy has been demonstrated to reduce subjective pain reporting.[9,10] Indeed, the proportion of patients in the trial by Li *et al.* experiencing moderate-to-severe pain, based on numerical scale reporting, was significantly reduced in patients with an epidural. Total opioid consumption was also lower in the epidural group, and opioids disrupt cortical processes that support cognition.[11] Epidural analgesia may also reduce systemic inflammation,[5] which, by extension, may reduce neuroinflammatory processes underlying delirium. While inflammatory markers were not assessed in the current study, epidural therapy nonetheless appeared to reduce delirium incidence concurrent with improved pain and reduced opioid consumption.

Although there is a paucity of data from clinical trials on the effects of epidural analgesia on delirium risk,

Image: A. Johnson, Vivo Visuals.

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the results of Li *et al.* should be considered in the context of past studies. A secondary analysis of a clinical trial focused on another intervention demonstrated that noncardiac surgery patients with postoperative epidural analgesia were 64% less likely to experience an episode of delirium compared to patients with intravenous and oral analgesic regimens.[9] Likewise, oral and intravenous opioid consumption was significantly reduced in patients with an epidural, as were subjective pain scores. Conversely, a small single-center randomized trial comparing postoperative patient-controlled epidural analgesia compared to patient-controlled intravenous anesthesia did not demonstrate a delirium risk reduction (26% *vs.* 24%, respectively), despite improved pain scores in the epidural group.[10] Cognitive function testing scores were, however, improved in the epidural group on the fourth and fifth postoperative day. In this trial, and the one conducted by Li *et al.*, sufentanil was the epidural opioid used, which is noteworthy given that epidural administration and intravenous administration result in similar plasma concentrations.[12] Given that opioids are associated with postoperative delirium, epidural solutions with relatively hydrophilic opioids (and less systemic absorption) may conceivably further reduce risk. Indeed, in the secondary analysis discussed above, hydromorphone was the most common epidural opioid used.[9] The choice of epidural opioid may thus impact delirium risk and should be taken into account in future study designs.

The study by Li *et al.* has a number of methodologic strengths. First, the authors are to be commended on successful epidural randomization, which requires support from surgical colleagues, patient willingness, and technical proficiency, among other challenges. The randomized nature of the study mitigates epidural selection bias. Second, delirium assessment strategies were rigorous. Research team members underwent initial delirium training by a psychiatrist, which was followed by additional delirium lectures, simulation training with actors, and repeated delirium assessment training until score agreement was reached with the psychiatrist. Training practices were then repeated throughout the year. Finally, delirium assessors were blinded to group allocation, further reducing bias.

However, important limitations warrant consideration as well. The overall incidence of detected delirium in the trial was surprisingly low (<5%), given that the reported incidence for older patients after major noncardiac, nonemergent surgery is typically around 20%.[1] One explanation may be that nonverbal delirium screening tools, like the Confusion Assessment Method for the Intensive Care Unit (used in the current study), demonstrate reduced sensitivity compared to verbal alternatives.[13] Less obvious cases of delirium may have evaded detection. Additionally, a continuous morphine infusion was used in the nonepidural trial arm. This drove an increase in opioid consumption that may also have increased delirium risk. Epidural opioid use was restricted to sufentanil, preventing analysis of different opioids on delirium risk.

Overall, the results presented by Li *et al.* are encouraging and supported by biologic plausibility. However, the highlighted limitations preclude firm conclusions. Follow-up studies are warranted with verbal delirium screening tools, comparator arms without continuous opioid infusions, and inclusion of epidural opioids other than sufentanil. The study does serve as a reminder that the central nervous system functions along a continuum, and neuraxial therapies may confer cognitive benefit.

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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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