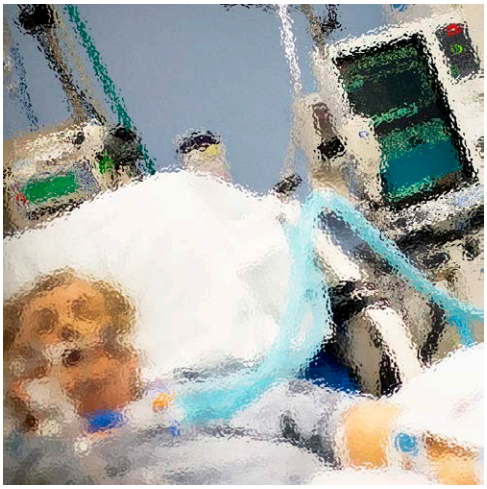
Baseline Vulnerabilities May Play a Larger Role than Depth of Anesthesia or Sedation in Postoperative Delirium

Pratik P. Pandharipande, M.D., M.Sc., Elizabeth L. Whitlock, M.D., M.Sc., Christopher G. Hughes, M.D., M.Sc.

Studies in mechanically ventilated patients have brought to the forefront the iatrogenic harm of deep sedation, particularly with continuous benzodiazepine infusions.[1,2] Interventional trials modifying sedation paradigms (*e.g.*, with nonbenzodiazepine medications)[3] and delivery patterns (*e.g.*, daily awakening trials, targeted light sedation),[4] as well as large-scale implementation trials of bundled supportive care (ABCDEF Bundle[5]; http://www.iculiberation.com, accessed August 1, 2021), have shown a decrease in sedative medication burden associated with clinically meaningful outcome benefits, including delirium, time on mechanical ventilation, and even mortality. The Society of Critical Care Medicine's Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption,[6] therefore, recommend targeting light sedation when needed, minimizing overall sedative medication exposure, and avoiding benzodiazepine infusions. With the high incidence and associated morbidity of postoperative brain dysfunction, there has been interest in utilizing similar techniques in the operating room. Unfortunately, it is unclear if the beneficial findings of reducing delirium by targeting lighter sedation in critically ill patients extrapolates to patients in the operating room undergoing general or regional anesthesia.



"Should we be surprised by the lack of an effect of depth of anesthesia or sedation on delirium outcomes during surgery, when studies in ICU patients have strongly suggested otherwise?"

In this issue of Anesthesiology, Brown *et al.* build on earlier work to elucidate the role of depth of sedation in the context of an anesthetic on delirium outcomes.[7] In the SHaping Anesthetic techniques to Reduce Postoperative delirium (SHARP) trial, investigators randomized 219 older patients undergoing lumbar fusion to either spinal anesthesia with propofol sedation titrated to a Bispectral Index (BIS) value greater than 60 to 70 (intervention) *versus* general anesthesia (control), where the anesthesiologist was blinded to the BIS values.[7] Patients were evaluated for delirium for the first 3 postoperative days using the Confusion Assessment Method. In the primary intention-to-treat analysis, median BIS values were 62 (interquartile range, 53 to 70) in the group that underwent spinal anesthesia with propofol sedation *versus* 45 (interquartile range, 41 to 50) in the group that underwent general anesthesia. Despite this, there were no statistically significant differences in delirium incidence rates: 25% in the spinal anesthesia with propofol group *versus* 19% in the general anesthesia group. Subgroup analyses factoring in age, comorbidities, and previous cognitive impairment did not yield any sufficiently powered results that would lend strong support to the use of one technique in favor of the other.

This study adds to the growing literature from randomized controlled trials that depth of anesthetic or sedation while undergoing regional anesthesia does not significantly alter delirium rates in the postoperative period in older patients. Two recent studies help contextualize this. In the ENGAGES (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes) study,[8] patients (aged older than 60 yr and undergoing major surgery) were randomized to receive electroencephalogram (EEG)–guided anesthetic administration

Image: J. P. Rathmell.

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(n = 614) or usual anesthetic care (n = 618). The median end-tidal volatile anesthetic concentration and median cumulative time with EEG suppression was significantly lower in the EEG-guided group than the usual-care group. Delirium during postoperative days 1 to 5 was not different in the two groups and occurred in 26% in the EEG-guided group and 23% in the usual-care group. The double-blind STRIDE (Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients) study[9] included older patients (aged 65 yr or older) who were undergoing nonelective hip fracture repair with spinal anesthesia and propofol sedation. Patients were randomized to heavier (Modified Observer's Assessment of Alertness and Sedation score of 0 to 2) or lighter (Observer's Assessment of Alertness/Sedation score of 3 to 5) levels of intraoperative propofol sedation. The overall incident delirium risk again was similar in both groups when measured on postoperative days 1 to 5.

Should we be surprised by the lack of an effect of depth of anesthesia or sedation on delirium outcomes during a surgical procedure, when studies in intensive care unit (ICU) patients have strongly suggested otherwise? Or are there fundamental differences in the patient populations, study design, and outcomes assessed that provide insight for future interventional trials? Baseline patient vulnerabilities may play the major role in development of delirium, with modifiable risk factors such as sedation/anesthetic depth and early mobilization, among others, providing some opportunity for targeting interventions.[10] Importantly, patients with greater vulnerabilities are probably more likely to benefit from addressing modifiable risk factors. The SHARP study patients had a median American Society of Anesthesiologists physical status classification of 2 (interquartile range, 2 to 3) and Charlson Comorbidity Index of 1 (interquartile range, 0 to 1), indicating a lower degree of comorbidity than ICU patients and highlighting a lower vulnerability risk. Like other studies in the operating room, including STRIDE,[9] the exposure to the intervention (deep *vs.* light sedation) was also brief (median, approximately 2 h) as compared with 2 to 3 days of sedation exposure in critically ill patients. Delirium was also not measured on postoperative day 0, a day where the contribution of sedation depth on delirium could have been higher.[11] These factors may help, in part, to explain the disparity in results between ICU and operating room studies. Additionally, currently identified surrogate markers of anesthetic or sedation depth using BIS or EEG may be inappropriate to target interventions aimed at addressing depth of anesthetic and sedation to make a significant impact on delirium outcomes. While there was a statistically significant difference between the groups in the SHARP trial[7] with regard to the BIS scores (62 in intervention; 45 in control), that difference may not be clinically meaningful in the context of the spinal anesthesia group still getting propofol in doses up to 125 mcg · kg^{-1} · min^{-1} (median highest dose, 80 mcg · kg^{-1} · min^{-1}), which may have contributed to higher-than-expected rates of delirium in the intervention. Future studies may help identify specific EEG patterns that are associated with worse delirium outcomes, allowing us to better focus interventions on a hypothetical vulnerable subpopulation (*e.g.*, the sensitive brain hypothesis, reduced cognitive reserve). ICU studies have shown that even a short duration of burst suppression (minutes) is associated with delirium after recovery from coma. The ENGAGES trial[8] was able to demonstrate a reduction in EEG suppression time from 13 min to 7 min, yet those 7 min may also be too much of an insult and something that perhaps can be avoided completely.

While the search for a surrogate marker of anesthetic or sedation depth with good specificity and sensitivity in the operating room is ongoing, adequately powered trials that help us understand the impact of anesthetic strategies on patients with high vulnerability and potential to benefit from modification of risk factors should be conducted. The current SHARP study was unfortunately powered assuming an almost 40% incidence of delirium and with an ambitious goal of reducing delirium by almost 50%, while in actuality the base rates of delirium were found to be much lower. This prevents a robust evaluation of statistical interactions between the interventions and key baseline vulnerabilities such as cognitive impairment, higher age, and comorbid status; although the cognitively impaired subgroup appeared to benefit from spinal anesthesia, the subgroup analysis itself was underpowered. Nonetheless, the authors' prespecified and *post hoc* subgroup analyses offer provocative hypotheses about the potential interactions of baseline cognitive impairment or of intrathecal morphine with the potential for harm or benefit of general anesthesia (some of which conflict with extant data in these areas). There is certainly more here that needs to be studied. Until we have stronger evidence to the contrary or higher fidelity measures to target anesthetic depth, it appears that baseline vulnerabilities and many determinants of the hospital course play larger roles in the multifactorial and complex underpinnings of delirium than the brief exposure to anesthetics and sedatives in the operating room does.

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Competing Interests

Dr. Hughes serves as a consultant for Sedana Medical (Danderyd, Sweden). The remaining authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Pandharipande: pratik.pandharipande@vumc.org

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