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Best Practices for Postoperative Brain Health: Recommendations From the Fifth International Perioperative Neurotoxicity Working Group

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Abstract

As part of the American Society of Anesthesiology Brain Health Initiative goal of improving perioperative brain health for older patients, over 30 experts met at the fifth International Perioperative Neurotoxicity Workshop in San Francisco, CA, in May 2016, to discuss best practices for optimizing perioperative brain health in older adults (ie, >65 years of age). The objective of this workshop was to discuss and develop consensus solutions to improve patient

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management and outcomes and to discuss what older adults should be told (and by whom) about postoperative brain health risks. Thus, the workshop was provider and patient oriented as well as solution focused rather than etiology focused. For those areas in which we determined that there were limited evidence-based recommendations, we identified knowledge gaps and the types of scientific knowledge and investigations needed to direct future best practice. Because concerns about perioperative neurocognitive injury in pediatric patients are already being addressed by the SmartTots initiative, our workshop discussion (and thus this article) focuses specifically on perioperative cognition in older adults. The 2 main perioperative cognitive disorders that have been studied to date are postoperative delirium and cognitive dysfunction. Postoperative delirium is a syndrome of fluctuating changes in attention and level of consciousness that occurs in 20%–40% of patients >60 years of age after major surgery and inpatient hospitalization. Many older surgical patients also develop postoperative cognitive deficits that typically last for weeks to months, thus referred to as postoperative cognitive dysfunction. Because of the heterogeneity of different tools and thresholds used to assess and define these disorders at varying points in time after anesthesia and surgery, a recent article has proposed a new recommended nomenclature for these perioperative neurocognitive disorders. Our discussion about this topic was organized around 4 key issues: preprocedure consent, preoperative cognitive assessment, intraoperative management, and postoperative follow-up. These 4 issues also form the structure of this document. Multiple viewpoints were presented by participants and discussed at this in-person meeting, and the overall group consensus from these discussions was then drafted by a smaller writing group (the 6 primary authors of this article) into this manuscript. Of course, further studies have appeared since the workshop, which the writing group has incorporated where appropriate. All participants from this in-person meeting then had the opportunity to review, edit, and approve this final manuscript; 1 participant did not approve the final manuscript and asked for his/her name to be removed.

CONSENT

Although international and regional practices regarding consent may vary, there was widespread agreement that older patients should be informed about perioperative neurocognitive disorder (PND) risks as part of the informed consent for anesthesia and/or surgery for 4 reasons.[1–3] First, the risks of PND are orders of magnitude more common than other risks about which anesthesiologists and surgeons consent patients, such as intraoperative mortality and intraoperative awareness with explicit recall.[4–6] Further, current consent discussions include other perioperative risks that we do not currently have the ability to prevent in all cases, such as postoperative stroke or myocardial infarction. Second, consenting patients about the risks of PND gives them and their families a realistic impression of their possible postoperative recovery course, and what their cognitive state may be in the days, weeks, and months after anesthesia and surgery. Third, educating patients about these risks can allow patients to plan effectively so they can either make important cognitively demanding decisions before anesthesia and surgery or delay making these decisions until several months afterward. Fourth, informing patients of these risks could help facilitate planning for measures to mitigate the risk of PND, such as encouraging family engagement and promoting early mobility.

Although there was some disagreement about this point, the majority of meeting participants thought that both anesthesiologists and surgeons should discuss these risks with patients, for 3 specific reasons. First, both anesthesia and surgery are thought to contribute to postoperative delirium and/or cognitive dysfunction.[1,2,7] Second, there is an emerging movement toward multidisciplinary "team" medicine (including surgeons, anesthesiologists, geriatricians, and others) and joint decision making regarding perioperative care (including consent discussions) in older patients.[8] Further, surgical and anesthetic "risks" are now understood to mean not only acute intraoperative risks such as bleeding but also longer-term "risks" such as PND (and their sequelae).

Another related question is when these consent discussions about PND risks should occur. Ideally such discussions should take place well before the day of surgery so that patients have the chance to learn about these risks in a non-pressured environment and have time to clarify any issues and ask questions. This is obviously challenging in the present environment, in which, many times, patients may not see their anesthesiologist before the day of surgery, and many consent discussions for both surgery and anesthesia occur on the day of surgery (and often in the hours or minutes beforehand).

Consensus Statement

"All patients over age 65 should be informed of the risks of PND including confusion, inattention, and memory problems after having an operation."

PREOPERATIVE NEUROCOGNITIVE ASSESSMENT

Preoperative cognitive impairment is a strong, preexisting risk factor for PND,[9–12] thus raising the question of whether a patient's cognitive function should be evaluated before surgery. The assessment of cognitive capacity is also important as the premise underlying informed consent is the presumed ability of patients to receive and process information, to ask questions, and to make an informed decision regarding their care. Anesthesiologists currently assess numerous other organ systems as part of routine preoperative evaluations via medical history, physical examination, and laboratory studies (Table 1). Because the central nervous system (CNS) is the target organ of nearly all anesthetic and analgesic drugs and CNS dysfunction plays a central role in PND,[1,2] it makes intuitive sense to assess the CNS before dramatically altering its function with anesthetic drugs. Further, assessing baseline cognitive function before surgery could help allow patient stratification for PND risk so that resources and interventions (such as intraoperative protocols to prevent PND) can be targeted at high-risk patients, similar to the way anesthesiologists stratify patients based on the function of other organ systems (such as New York Heart Association status or model for end stage liver disease [MELD] scores). Because many age-related comorbidities (eg, hypertension, diabetes mellitus, and obstructive sleep apnea[13]) also increase the risk of cognitive impairment even outside the perioperative setting, it is particularly important to assess cognition in older adults and in any patient with these comorbid conditions. Identifying patients with mild preoperative cognitive impairments (and who are at increased PND risk), but who still retain decision-making capacity, could allow discussions with these patients about PND risk. These preoperative discussions could help patients at increased

PND risk plan ahead, such as by making important decisions before surgery or delaying them until several weeks or months after surgery.

However, assessing baseline CNS function is complex because of the wide variety of cognitive processes performed by the brain. It is also neither practical nor appropriate to conduct a lengthy neuropsychological assessment during a routine preoperative clinic visit. Nonetheless, brief cognitive screening tests (see Table 2 for a brief, nonexhaustive list) are feasible to use in the preoperative screening clinic[14] and can help detect cognitive impairment and thereby identify patients at increased risk of postoperative complications.[14,30] Future studies should compare feasibility, predictive power, and clinical usefulness of these various brief cognitive screening tests, to help determine which is the most useful in the perioperative setting. In the meantime, using any of these tests can help identify a subset of patients who could be referred for more detailed preoperative neurocognitive assessment. Similarly, patients with subjective cognitive complaints could also be referred for a more extensive workup, just as anesthesiologists only order cardiac stress tests on a small subset of surgical patients.

Identifying patients with preoperative cognitive impairment could also help target these high-risk patients for interventions to minimize PND. Such interventions might include improvement of sleep and nutrition hygiene, avoidance of specific drugs, specific intraoperative management strategies[31] (see below), rapid return of glasses and hearing aids, and family engagement and orientation strategies.[32] Identifying at-risk patients for these targeted interventions may reduce the risk of PND by up to 40%.[31,32] Further, if anesthetic management strategies are identified that make PND less likely, then these strategies may become the default approach for all elderly patients.

Consensus Statement

"Baseline cognition should be objectively evaluated with a brief screening tool during preoperative evaluation in all patients over the age of 65 and in any patient with risk factors for preexisting cognitive impairment."

INTRAOPERATIVE MANAGEMENT

Numerous studies have demonstrated that specific intraoperative anesthetic or physiologic variables are associated with increased risk for certain types of PND (such as delirium or postoperative cognitive dysfunction [POCD]), and some studies have suggested that the use of specific drugs, techniques, or monitors may alter the risk of these disorders. The meeting participants uniformly agreed that the current literature is insufficient to recommend any particular anesthetic to reduce PND risk in older adults. Nonetheless, there was widespread agreement that the medications listed in Table 3 should be used cautiously or even avoided in older patients, given their known propensity to contribute to PND and/or other forms of cognitive dysfunction in older adults outside the perioperative care setting.

Anesthetic Drugs

There is little evidence that any particular volatile anesthetic agent is associated with an altered risk of PND. Nonetheless, there are clearly age-dependent changes in volatile anesthetic sensitivity. The minimum alveolar concentration (MAC) of a volatile anesthetic necessary to prevent movement in response to surgical incision in 50% of patients declines by ≈6% per decade after 30 years of age.[34,35] Because volatile anesthetics have one of the narrowest therapeutic indices of any drug used in modern medicine,[36,37] avoiding volatile anesthetic overdose by closely monitoring the age-adjusted MAC fraction is critical to avoid side effects of these drugs[38] and may even help to lower delirium rates.[31,39] For example, in the cognitive dysfunction after anesthesia (CODA) trial, a 39% decrease in the age-adjusted end-tidal MAC fraction (ie, the inhaled anesthetic dose received by patients) was associated with a 31% reduction in cognitive dysfunction at 3 months after surgery and 35% reduction in postoperative delirium.[31] Thus, there was widespread agreement among the participants that anesthesiologists should use age-adjusted MAC fraction in older adults to adjust end-tidal volatile anesthetic concentration during surgery, which at least provides a population-derived starting point for dosing inhaled anesthetics.

Similarly, it may seem intuitive that using a regional anesthetic technique or nerve block to either complement or replace a general anesthetic could help decrease systemic anesthetic administration and thereby might lower the incidence of PND. Yet, this intuition is largely unsupported by data because the majority of studies that have examined this issue have not found an increased risk of delirium or POCD after general as compared to regional anesthesia.[40–42] However, many of these studies were confounded by the administration of high doses of intravenous sedatives in the regional anesthesia groups. In fact, many patients in the regional anesthesia groups in these studies may have actually been in a state of general anesthesia from a neuroscience perspective (ie, the patient was sufficiently unconscious during a regional technique as if he/she were receiving general anesthesia). Nonetheless, even in 1 randomized controlled trial that rigorously ensured that patients in the regional group did not receive any intravenous sedation, there was still no difference in delirium rates among the regional versus the general anesthesia groups.[42] Thus, the current literature does not support the recommendation that a regional anesthetic technique should be used in place of (or in addition to) general anesthesia to reduce delirium or PND rates. Similarly, a number of studies have examined whether using specific drugs to maintain general anesthesia affect the rates of various types of PND, but no clear consensus recommendations have emerged from these studies.[43–49]

Intraoperative EEG Monitoring and Anesthetic Titration

Several studies have also examined whether anesthetic titration in response to processed electroencephalography (EEG) monitoring might lower the risk of delirium or POCD. Two studies have found a statistically significant decrease in delirium rates when anesthetic “depth” was titrated based on monitoring with the Bispectral Index (BIS; Medtronic, Minneapolis, MN) monitor (a processed EEG monitor).[31,39] Four studies have examined the use of processed EEG monitoring with BIS for POCD prevention, and the results have been mixed. One study found lower POCD rates 3 months after surgery in patients who underwent BIS monitoring,[31] a second study found no effect,[39] and 2 other studies conversely found that patients with lower processed EEG values actually had improved cognition[50] or lower rates of delirium and POCD.[51]

However, the BIS monitor uses a proprietary algorithm and has never been specifically validated for use in older adults. Recent theoretical[52] and empirical work[53] suggests that the BIS algorithm may report erroneously high values in most older adults (which could then lead providers to administer unnecessarily high anesthetic dosage in older patients) and may also report lower than normal values in patients with preexisting cognitive impairment or dementia.[54,55] Further, there is a roughly flat relationship between end-tidal age-adjusted volatile anesthetic concentrations and BIS values over the clinically used range of volatile anesthetics (ie, 0.5–1.5 MAC).[53,56] This roughly flat relationship between MAC fraction and BIS values, and the other issues with the BIS discussed above, suggests that titrating anesthetic concentration to the BIS number may be challenging in older adults. This point may explain the lack of large anesthetic dosage differences between patients in the BIS-guided versus BIS-blinded arms of some of the studies discussed above.[39]

Taken altogether, this literature raises doubt as to the use of currently available processed EEG monitors to prevent delirium or POCD. Nevertheless, several retrospective studies have found an association between raw EEG signal parameters (such as burst suppression, a state of intermittent electrical brain silence) and postoperative delirium,[57,58] which raises the possibility that either titrating anesthetic delivery to avoid burst suppression or in response to other raw EEG parameters[59] (such as those discussed at icetap.org and eegforanesthesia.iars.org) could help reduce the risk of delirium or POCD. Several current studies are examining this possibility[60–62]; the results of these studies may provide further guidance on how raw EEG-based anesthetic titration might help lower the rates of PND and improve postoperative cognitive function. While there are clearly challenges in the use of current processed EEG monitors, EEG-based anesthetic titration has nonetheless been shown to lower delirium and POCD rates in multiple independent randomized controlled trials (ie, level 1 evidence). Thus, there is strong support for the general principle of EEG-based anesthetic titration to reduce PND rates in older adults (Table 4).

Anesthetic/Surgical Physiology

There was a general consensus to avoid intraoperative hypotension (using parameters relative to each patient's baseline blood pressure), largely with a goal of maintaining cerebral perfusion. Several studies have found an association between intraoperative hypotension and increased incidence of delirium or cognitive change[63–65] after surgery, although other studies have found conflicting evidence.[66,67] However, different studies have used different thresholds to define hypotension; a systematic review found over 140 different definitions for hypotension in the literature.[68] This ambiguity highlights the potential importance of defining hypotension based on individualized patient monitoring rather than population cutoffs. Furthermore, there is a right shift in the cerebral autoregulation curve in patients with chronic hypertension, and because many older patients have chronic hypertension, it is important to titrate blood pressure parameters relative to each patient's baseline blood pressure while considering head height relative to the blood pressure monitoring site.

Near-infrared spectroscopy (NIRS) is commonly used during cardiac surgery as a real-time continuous monitor of cerebral perfusion. In several studies, an intraoperative decline in

NIRS values has been associated with postoperative delirium and/or cognitive change.[69,70] However, general limitations of these studies include small size, short follow-up, and inconsistent results.[71] One randomized study examined the benefit of an intervention protocol based on NIRS values and demonstrated an improvement in major morbidity and mortality in cardiac surgery patients in the intervention arm.[72] Importantly, cognitive outcomes were not measured, and these results[72] have not been reproduced. However, 2 pilot trials have established feasibility for future, large randomized controlled trials using NIRS to reduce PND,[73,74] and another study found that the combination of BIS-based and cerebral oximetry–based anesthetic titration reduced POCD in older adults.[75] Overall, though, the meeting participants thought that the evidence in support of NIRS to reduce PND was less strong than the evidence in support of EEG-based anesthetic titration to reduce PND.

An alternative method of measuring cerebral perfusion is real-time monitoring of cerebral autoregulation, which can be used to maintain mean arterial pressure above the lower limit of cerebral autoregulation. In patients with traumatic brain injury, deviations of blood pressure above or below the limits of autoregulation have been associated with poor neurological outcomes.[76] An investigation in a cardiac surgery population demonstrated that the mean arterial pressure at the lower limit of autoregulation varied widely and could not be predicted using patient variables.[77] Further, deviations of blood pressure below the lower limit of autoregulation during cardiac surgery have been associated with both acute kidney injury[78] and major morbidity and mortality,[79] while deviations above the upper limit of autoregulation have been associated with delirium.[80] Together, these results underscore the need for individualized monitoring of cerebral perfusion, and the need for further studies to elucidate the effect of reduced cerebral perfusion on neurocognitive outcomes.

Consensus Statement

"Anesthesiologists should monitor age-adjusted end-tidal MAC fraction, strive to optimize cerebral perfusion, and perform EEG-based anesthetic management in older adults. Further research is needed to evaluate and compare specific brain function monitors, methods, and approaches."

POSTOPERATIVE FOLLOW-UP AND MANAGEMENT

Although it is clear that many of our older patients will experience PND after intraoperative care, there was little consensus on who should follow these patients and/or manage these problems in the postoperative period. Outside the pain clinic or intensive care unit settings, most anesthesiologists only see their postoperative patients a day or 2 after surgery for a brief postoperative check. Because many PND cases do not become clinically apparent until after this point (if at all), most anesthesiologists likely will remain unaware of these cognitive issues in their patients. Further, anesthesiologists are physicians who are primarily trained in acute intraoperative and perioperative management of surgical patients, and most anesthesiology residency programs do not cover the diagnosis or management of cognitive problems such as PND.

However, there was a widespread consensus among participants that we need more studies on how to optimize the postoperative care of these patients and how to best manage PND. Such studies should evaluate the efficacy, feasibility, and cost-effectiveness of multiple different strategies to assess outcomes, ranging from in-person clinic visits to telephone calls/telemedicine to automated electronic assessment tools (ranging from apps to automated phone calls), to both physical and cognitive exercise programs, sleep hygiene improvement, and/or drug treatment approaches. Further, because multiple other elements of postoperative recovery (such as pain, functional recovery, ability to exercise and resume activities, etc) also have delayed resolution, postoperative follow-up assessments should measure multiple domains of postoperative recovery in parallel. The recent development of standardized nomenclature and tools for postoperative outcome assessments can further aid in comparing outcome measures across studies, institutions, and even countries.[81]

Consensus Statement

"More studies are needed to evaluate the efficacy, feasibility, and cost-effectiveness of various strategies to assess short- and long-term cognitive outcomes after hospital discharge, to optimally manage these disorders, and to clarify who should follow patients after surgery for these disorders and what patients should be told about the current understanding regarding recovery from these disorders."

CONCLUSIONS

PND are significant public health issues, over 16 million Americans over 60 years of age, undergo anesthesia and surgery each year, and studies suggest that >10%–40% of these patients will develop a form of PND after perioperative care.[2] This suggests that each year there are likely over 1.6 million older Americans who suffer from PND, making these the most common postoperative complications in older adults. Our hope is that this summary of expert opinions, together with the additional studies called for here, can serve in the future as the basis for a more formalized set of evidence-based recommendations for minimizing the impact of PND and optimizing postoperative brain health. We also hope that the new standardized PND nomenclature will facilitate discussion of intermediate- versus long-term postoperative neurocognitive disorder risks for individual patients. This article is based on informal, in-person discussions and consensus at our 2016 meeting, and subsequent thorough review of this manuscript by participants at that 2016 meeting. Future recommendations and practice guidelines should be based on formal grading of the level of evidence and practical consideration of how these recommendations and guidelines can be incorporated into perioperative medicine practice.

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APPENDIX

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Table 1.

Fifth International Perioperative Neurotoxicity Workshop: Issues and Initial Questions

Consent: Should the risks of postoperative delirium and cognitive dysfunction be included in consent discussions with older patients? If so, who should have these consent discussions (ie, anesthesiologists, surgeons, both, neither), and when and where should these discussions take place?
Preoperative neurocognitive assessment: Should cognitive function be assessed before surgery in older adults? If so, how, when, and by whom?
And should such assessments be performed on everyone or only on select high-risk patients?
Intraoperative management
Anesthetic technique to maximize postoperative brain health: —regional versus neuraxial versus general or combinations thereof?
Particular drugs to use or to avoid to maximize postoperative brain health: TIVA versus inhaled agents, one inhaled agent versus another, adjunct agents to avoid (ie, anticholinergics, steroids, benzodiazepines)?
Monitoring: are there particular monitors that should be used or considered to maximize postoperative brain health, ie, BIS, Sedline (Masimo, Irvine, CA), raw EEG, cerebral oximetry?
Postoperative follow-up: What sort of postoperative follow-up should be performed to assess postoperative brain health and when? If patients have postoperative cognitive concerns, what should be done? To whom and where should the patient be referred?

Abbreviations: BIS, Bispectral Index; EEG, electroencephalography; TIVA, total intravenous anesthesia.

Table 2.

Brief Cognitive Screening Tools

Tool/Test	Advantage	Disadvantage	Sensitivity[a]	Specificity[a]	Time to Administer
Minicog[14–18]	Brief, minimal language, education, race bias	Use of different word lists may affect scoring	76–100 (54–100)	54–85.2 (43–88.4)	2–4 min
MoCA[19–22]	Can identify mild cognitive impairment, available in multiple languages	Education bias, limited published data	n/a	n/a	10–15 min
MMSE[18,23,24]	Widely used and studied	Subject to age and cultural bias, ceiling effects	88.3 (81.3–92.9)	86.2 (81.8–89.7)	7–10 min
Clock-drawing test[18,25]	Very brief	No standards for administration and scoring	67–97.9 (39–100)	69–94.2(54–97.1)	<2 min
Verbal Fluency Test[18,26]	Brief	Cut point not obvious	37–89.5 (19–100)	62–97 (48–99)	2–4 min
CODEX[27–29]	Brief	Less well studied	81%–93%	81%–85%	≤3 min

Abbreviations: CODEX, Cognitive Disorder Examination; MMSE, Mini-Mental State Examination; MoCA; Montreal Cognitive Assessment; n/a, not applicable.

[a] Sensitivity and specificity values are for the detection of cognitive impairment or dementia

Table 3.

Medications Commonly Given by Anesthesiologists That Should Be Avoided or Used With Caution in Patients Over 65 Year of Age[33]

Medication or Class of Medication	Examples	Rationale for Avoiding
First-generation antihistamines	Diphenhydramine	Central anticholinergic effects
Phenothiazine-type antiemetics	Prochlorperazine, promethazine	Central anticholinergic effects
Antispasmodics/anticholinergics	Atropine, scopolamine	Central anticholinergic effects
Antipsychotics (first and second generation)	Haloperidol	Risk of cognitive impairment, delirium, neuroleptic malignant syndrome, tardive dyskinesia
Benzodiazepines	Midazolam, diazepam	Risk of cognitive impairment, delirium
Corticosteroids	Hydrocortisone, methylprednisolone	Risk of cognitive impairment, delirium, psychosis
H_2-receptor antagonists	Ranitidine	Risk of cognitive impairment, delirium,
Metoclopramide		Extrapyramidal effects
Meperidine		Neurotoxic effects
Skeletal muscle relaxants	Cyclobenzaprine	Anticholinergic effects

Abbreviation: H_2, histamine 2 receptor.

Table 4.

Intraoperative Recommendations to Promote Postoperative Brain Health

Avoid centrally acting anticholinergics, benzodiazepines, meperidine, and other drugs listed in Table 3
Avoid relative hypotension
Maintain normothermia
Monitor age-adjusted end-tidal MAC fraction
Use EEG-based intraoperative brain monitoring to titrate anesthetic administration

Abbreviations: EEG, electroencephalography; MAC, minimum alveolar concentration.