Controversies in the Perioperative Management of the Vulnerable Brain

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Published 19 May 2026 DOI: 10.28923/atotw.572

KEY POINTS

- Extended preoperative examination is recommended in all elderly patients undergoing major elective surgeries.
- There is no strong evidence that cognitive prehabilitation prevents perioperative neurocognitive disorders (PNDs); however, it can improve cognitive reserve.
- The choice of primary anaesthetic technique (General Anaesthesia/Neuraxial Anaesthesia) and use of Total Intravenous Anaesthesia/inhalational maintenance is based on the type of surgery, patient condition, and practitioner preferences and does not influence PND outcomes.
- Electroencephalogram monitoring should be practiced to titrate depth of anaesthesia for intravenous and inhalational anaesthetic techniques to preserve brain health in vulnerable populations.
- Multimodal analgesia utilizing nonopioids and regional techniques allow for minimizing opioids to the lowest effective dose.
- No specific drugs have been routinely recommended to prevent PNDs, but dexmedetomidine has shown encouraging results.

INTRODUCTION

Surgery and anaesthesia are stressful events that can trigger a host of neurohormonal immune responses.[1] Disruption of the blood brain barrier makes the geriatric brain highly vulnerable to these stressors resulting in perioperative neurocognitive disorders (PND).[2] The updated nomenclature of PNDs is presented in the consensus recommendation statement by the Perioperative Brain Health Group[3] with aetiology and pathophysiology described elsewhere.[4] The current tutorial adds to the background provided in ATOTW Tutorial No. 571 and focuses on controversies in the perioperative management strategies for preservation of brain health in the fragile adult brain.

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TAKE ONLINE TEST

PREOPERATIVE ASSESSMENT

Preoperative assessment of vulnerable individuals encompasses extended preoperative evaluation for risk assessment and stratification.[5] This includes but is not limited to cognitive screening, frailty assessment, psychosocial screening, and delirium assessment. Cognitive screening tools that are validated to be used by anaesthesiologist in the preoperative period are mini-mental status examination (MMSE), Clock drawing test (CDT), and Mini-Cog.[6] Among them, American College of Surgeons and American Geriatric Society practice guidelines strongly recommends Mini-Cog.[7] Further, The Society for Perioperative Assessment and Quality Improvement (SPAQI) recommends Months backward test (MBT), Short-Blessed Test, Telephone Interview of Cognitive status (TICS), Time & Change (T&C) test for cognitive screening, and Instrumental activities of Daily Living (IADL) for functional status of the individual.[8] However, the choice of test in clinical practice depends on educational status, ease of use, and time constraints. Table summarizes the cognitive tests that can be used in perioperative period. The major drawback of these tests is that the normative scores vary according to age, educational status, language, and ethnicity. Therefore caution is advised before interpretation. For delirium assessment, Perioperative Brain Health Initiative (PBHI) recommends 4 A's (Arousal, Attention, Abbreviated mental test, and Acute change) test and confusion ssessment method (CAM) in all high-risk older patients before emergency surgery.[9] Overall, the American Society of Anaesthesiologist (ASA) 2025 practice advisory, recommends extended preoperative evaluation in high-risk individuals with the qualification that there is low strength of evidence regarding the benefit of such assessments.[10]

COGNITIVE PREHABILITATION

This is the process of enhancing the cognitive capacity and reserve of participants through targeted interventions before major elective surgeries. The interventions target specific cognitive domains like memory, attention, and executive function. They are administered to the patient through computer-based or written training under supervision of medical personnel or can be self-administered. In a recent meta-analysis by He et al (2024), involving six studies with sample size of 645 participants, the authors concluded that there is currently no evidence of the effectiveness of cognitive prehabilitation on cognitive outcomes.[11] This must be interpreted in the context of varied protocols involving duration of training, methodology, educational status, age of patient, and type of intervention. The American Society of Anesthesiologists 2025 practice advisory also does not currently advocate any specific cognitive intervention to prevent PNDs.[10] Nevertheless, not undermining the importance of cognitive capacity building, the guideline directs for better quality studies. In this context, the results of the PReoperative Exercise to Decrease PostoperAtive Complications Rates and Disability scorEs (PREPARE) trial, a multicenter, randomised control trial (RCT) that aims to understand the effectiveness of prehabilitation in elective non-cardiac, non-neurologic and non-orthopaedic surgeries, are awaited.[12]

Test	Comment	Advantages	Limitations
CDT*	Moderate to high sensitivity for dementia. Low scores = Major NCD	Ease of administration, Minimal resources, less administration time	Less evidence of utility of command component
Mini-Cog*	Best screening tool Total score = 5 ≤2 = Cognitive impairement.	Ease of administration	Qualitative and over simplistic clock drawing test
MMSE*	24–30: Mild NCD. <24: Major NCD	High predictive value for POD Multiple cognitive domains can be tested	Longer time of administration Copyrighted
MBT*	<37% correct responses = major NCD 37-87% correct responses = Mild NCD	Ease of administration	Only subcortical-frontal functions can be assesed.
SBT*	>3 recall errors = Major NCD Sensitivity = 0.71 Specificity = 0.56	Ease of administration Free availability	Only memory domain assesed
TICS*	Maximum score = 40 <34 = Mild NCD <28 = Major NCD Sensitivity = 0.94 Specificity = 1.0	Can be administered over phone	Availability of care giver as Proctor

Table. Tests for identification of vulnerable brain. *Use with caution in individuals with lower formal education and in patients with language or comprehension difficulties. Clock drawing test (CDT), Mental status examination (MMSE), Mini-Cog, Months backward test (MBT), Short-Blessed Test, Telephone Interview of Cognitive status (TICS), Time & Change (T&C), NCD: Neurocognitive disorders; POD: Post operative delirium

INTRAOPERATIVE STRATEGIES

Intraoperative strategies like primary anaesthesia technique, adjunct regional anaesthesia (RA), drugs used, and monitoring techniques may affect cognitive outcomes. In the following paragraphs, these factors and the controversies are individually described.

General Anaesthesia (GA) vs Neuraxial Anaesthesia (NA)

GA in vulnerable individuals is subject to debate because of the effect of anaesthetic drugs on physiologically frail systems of the elderly. Usual doses of inhalational and intravenous drugs cause profound sedation and hypnosis as evidenced by burst suppression on Electroencephalography(EEG).[13] This high sensitivity of the brain combined with renal, hepatic, and respiratory compromise in elderly individuals receiving GA question its use as a primary anaesthetic technique. Thus, NA has emerged as alternate primary anaesthetic technique especially in lower limb orthopaedic surgeries. A recent RCT comparing GA vs NA in elderly individuals undergoing lower limb orthopaedic surgeries reported beneficial effect of NA.[14] However hemodynamic compromise and regular use of anticoagulants and antiplatelets in the context of central neuraxial blockade pose challenges for pursuing NA. Supporting this, recent meta-analysis did not show benefit of either GA or NA in preventing postoperative neurocognitive disorders.[15] Overall, the ASA practice advisory 2025[10] and PBHI[9] recommend that the primary anaesthetic technique is based on type of surgery, patient condition and practitioner, and patient preferences with shared decision making. There is scope for designing large studies with robust, standard protocols to explore long-term cognitive outcomes in vulnerable brains comparing GA and NA techniques.

Total Intravenous Anaesthesia (TIVA) vs Volatile Agents

Inhalational anaesthetic agents have a theoretical risk of neurotoxicity in vulnerable brains.[16] On the contrary, TIVA with propofol maintains hemodynamic stability and ensures smooth emergence. However, evidence from large RCTs[17] and meta-analyses[18] suggests no superiority of either technique on cognitive outcomes. Results from two large ongoing clinical trials, USA (Trajectories of Recovery after Intravenous propofol versus inhaled VolatilE anaesthesia-TRIVE)[19] and UK (Volatile vs Total intravenous Anaesthesia for major non-cardiac surgery: a pragmatic randomised trial-VITAL),[20] will provide better insights. To date, the ASA practice advisory 2025,[10] PBHI,[9] European Society of Anaesthesiology (ESA) guidelines[21] on postoperative delirium (POD), and Scottish Intercollegiate Guidelines Network (SIGN)[22] recommend either TIVA or inhalational agents. Alongside the guidelines advocate EEG-based depth of anaesthesia monitoring to prevent burst suppression, indicative of very deep planes of anaesthesia, while using either technique.

DRUGS

Dexmedetomidine: Dexmedetomidine is a central Alpha 2 agonist acting on the locus coeruleus causing sedation. It is known to inhibit neuroinflammation by inactivating microglial activation and reducing neuronal apoptosis. It also improves synaptic plasticity and prevents blood-brain barrier disruption and has the potential to prevent postoperative NCDs.[23] It is used in a loading dose of 1 mcg/kg (10 minutes before induction) and infusion dose of 0.2–0.7 mcg/kg/hr.[25] The beneficial effect of dexmedetomidine in preventing neurocognitive disorder (NCD) is supported by two meta-analyses.[24,25] However, in geriatric patients, dexmedetomidine is known to cause hypotension and bradycardia. ASA practice guidelines (2025) and ESA guidelines recommend the conditional use of dexmedetomidine for prevention of POD in high-risk vulnerable individuals.[10,21]

Benzodiazepines: Benzodiazepines are GABA agonists used for sedation, hypnosis, and anxiolysis. Short-acting benzodiazepines like midazolam are used as premedication for this purpose. Their use in older adults is controversial because of their known side effects of cognitive impairment and risk of delirium.[26] However, their use as premedication is supported by RCTs which showed lack of association of low-dose intravenous midazolam with POD.[27] American Geriatrics Society and ESA[21] recommends guarded use of short-acting benzodiazepines as premedication and the ASA (2025) practical guidelines[10] advise weighing individual risk vs benefit.

Recently, remimazolam, a novel ultrashort-acting benzodiazepine, which is also a GABA agonist, has been introduced for use in the perioperative period. It has stable hemodynamic effects and ameliorates neuropathic pain by limiting production of proinflammatory markers and ischemic reperfusion injury. It also blocks activation of microglia and astrocytes with potential to prevent PND.[28] It can be used for procedural sedation as well as with GA. Recent metanalyses showed remimazolam was beneficial in preventing postoperative NCDs,[29,30] but with a low level of evidence. Further, there is no consensus recommendation for regular use in high-risk individuals.

Esketamine: Esketamine, an S-enantiomer of ketamine, is a NMDA antagonist and is known to have a profound effect on hippocampal synaptic plasticity, minimising surgical stress response and decreasing neuroinflammatory markers.[31] A dose of 0.2–0.5 mg/kg is recommended during induction and 0.2–0.5 mg/kg/hr for maintenance. In a recent meta-analysis by Lin et.al, esketamine decreased the incidence of POD and postoperative NCD.[32] However, there is no current consensus for use of esketamine for POD prevention.

Multimodal pain management: Postoperative pain significantly contributes to postoperative NCD. This implies that optimal pain management strategies can be adopted in vulnerable patients. Multimodal pain management with various pharmacological (NSAIDS, steroids, peripheral nerve blocks) and non-pharmacological measures (acupuncture, transcutaneous electrical nerve stimulation[33]) administered simultaneously through different routes minimises opioid use and may prevent PND.

Anti-inflammatory drugs: Systemic/local inflammation triggered by surgery leads to activation of pain pathways, which in turn contributes to POD. Steroids and non-steroidal anti-inflammatory drugs can effectively reduce pain. Perioperatively dexamethasone[34] is commonly used for prevention of PNDs. Conclusions from meta analyses have been conflicting . Xie et al showed no beneficial effect on PND,[35] yet a recent meta-analysis concluded there were beneficial effects.[36] Recommendations from the Fifth International Perioperative Neurotoxicity Working Group does not support the use of steroids for preventing PND.[37] NSAIDS such as parecoxib,[38] and intravenous paracetamol[39] have been shown to effectively reduce the incidence of POD, but there appears to be no differences in long-term cognitive outcomes.[40] To date, there is no consensus guidelines for prophylactic use of steroids or NSAIDS in vulnerable individuals for prevention of PND.

Peripheral nerve blocks (PNB) as adjuncts to GA for postoperative pain management can reduce the incidence of POD. This was described in a recent metanalysis; however, there is huge variation in the analysed studies.[41] As the strength of the evidence is weak, there are no consensus guidelines.[30] Further, multimodal pain management with use of opioids at the lowest effective dose is recommended by PBHI.[9] Other drugs like magnesium and lignocaine have been investigated for prevention of PND with no apparent beneficial effect.[42,43]

Drugs to be avoided: Anticholinergics with central effects like diphenhydramine, promethazine, and atropine are to be avoided in the perioperative period in vulnerable individuals.[37] PBHI also recommends against the use of pethidine and advocates guarded use of opioids in postoperative pain management.[9]

OTHER MEASURES

Fluid management: The importance of goal-directed fluid therapy (GDFT) as brain protective strategy in preventing post-operative NCDs was studied by Wu et al (2024)[44] and Fuqiu et al (2023),[45] where the authors showed GDFT to be effective in preventing POD as against conventional fluid management. The results are attributed to a less intense systemic inflammatory response. However, long-term benefits are not known.

MONITORING

Intraoperative monitoring also plays a crucial role in preventing NCD. Commonly used monitoring strategies in prevention of PND are depth of anaesthesia monitoring, regional cerebral oxygen saturation (rSO2) monitoring, blood pressure, and temperature.

Depth of anaesthesia monitoring: Elderly individuals are more vulnerable to the effects of anaesthetic agents. Inadvertent use of maintenance agents resulting in deeper planes of anaesthesia leads to poorer cognitive outcomes.[46] Depth of anaesthesia monitoring guides the anaesthesiologist to adequately titrate the dose of maintenance agents. EEG is commonly used to monitor depth of anaesthesia. Processed EEG indices such as bispectral index (BIS), entropy, and patient safety index (PSI) provide information about depth of anaesthesia.[47] However, interpretation is not reliable in older and vulnerable individuals because of reduced cortical activity and low EEG power.[48] Burst suppression from raw EEG interpretation and density spectral array (DSA) interpretation may be more useful in this regard. Several metanalyses of RCTs found EEG-based depth of anaesthesia monitoring to be beneficial for prevention of POD.[49,50] ESA guidelines advocate mandatory use of depth of anaesthesia monitoring for all vulnerable patients undergoing major surgeries,[21] emphasizing the role of processed EEG indices as well as burst suppression indices in prevention of POD. Though the role of depth of anaesthesia monitoring on long-term cognitive outcomes is currently unclear, American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes: Electroencephalography[51] recommends anaesthesiologists maintain proficiency in EEG interpretation and advocate EEG to be part of vital organ monitoring. SIGN guidelines recommend depth of anaesthesia monitoring in all patients over 60 years under GA for surgery expected to last for more than 1 hour.[22]

Blood pressure: Good cerebral perfusion is a prerequisite for cerebral function. Maintaining Mean Arterial Pressure (MAP) above threshold is a commonly employed brain protective strategy in elderly patients who have compromised cerebral autoregulation. However, there is no established threshold of MAP to prevent NCD.[52] Recent meta-analysis did not show any protective effect of preventing hypotension on POD or postoperative NCDs[53] and there are currently no consensus guidelines on this.

Temperature: In the perioperative setting, hypothermia is a risk factor for delirium. Recent meta-analysis on effect of temperature on PND supported normothermia.[54] Further Recommendations from the Fifth International Perioperative Neurotoxicity Working Group recommend normothermia.[37]

Regional cerebral oxygen saturation (rSO2) monitoring: Cerebral oximetry is a safe non-invasive method of estimating cerebral perfusion using near-infrared spectrograph (NIRS). A drop in rSO2 value to 15%–20% of baseline intraoperatively is

known to produce significant decline in cognitive performance postoperatively.[55] Routine use of rSO2 is not indicated even in high-risk individuals. PBHI reports contentious efficacy of rSO2 monitoring for preventing POD and long-term cognitive outcomes.[9]

POSTOPERATIVE CONSIDERATIONS

Delirium

Identification of delirium in the immediate postoperative period is critical. Postoperatively PBHI recommends 4 A's test and CAM test to be done at the time of discharge from recovery room and twice daily till Day 5 or discharge.[9] Non-pharmacologic interventions are the first choice for prevention and management of POD. Awakening and Breathing Coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family engagement (ABCDEF bundle)[56] and 4 M's (medications, mobility, mentation, and "what matters to you" [understanding a patient's goals of care]) have high efficacy in preventing and managing delirium.[9] Regarding pharmacological interventions, there is no consensus agreement on use of dexmedetomidine, melatonin or ramelteon (a selective melatonin receptor agonist) for delirium prophylaxis.[10] Antipsychotics like haloperidol and risperidone can be used in the setting of violent behaviour or severe hallucinations. Benzodiazepine use is not indicated for routine management of delirium; however, it may play a role in delirium associated with substance withdrawal.[10]

Delayed Neurocognitive Recovery (dNCR) and Post-Operative NCDs

For the establishment of post operative NCD diagnosis, cognitive status of the patient is assessed in the postoperative period by MMSE, Minicog, and CDT. The diagnosis of new onset cognitive dysfunction can be derived by using the standard deviation method[57] or Z score method.[58] Patients with new onset cognitive dysfunction in the postoperative period can be referred for cognitive retraining and may need specialist geriatric, neurological, or psychological referral for follow-up.

SUMMARY

The current tutorial discusses the controversies in perioperative management of the vulnerable brain. The latest ASA guidelines and PBHI recommend extended preoperative examination in vulnerable individuals, which includes cognitive screening and frailty assessments for risk stratification. Cognitive prehabilitation has not yet been shown to have beneficial effects on NCD. There is no conclusive evidence regarding the superiority of primary anaesthetic technique or the type of maintenance agents; however, the role of EEG in depth of anaesthesia monitoring is highlighted in consensus recommendations. Early identification of POD is pivotal and non-pharmacological interventions are the first line in prevention and management. Dexmedetomidine use in perioperative period is supported by very low evidence and should be used cautiously in vulnerable high-risk individuals.

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