# Perioperative Approaches to Decrease the Incidence of Postoperative Cognitive Decline and Postoperatve Delirium in Older Patients

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The American population is ageing. Concurrently, surgical interventions are being increasingly used as treatment for medical conditions, including in older adults. As such, there is an increasing need to define delirium and postoperative cognitive dysfunction (POCD), identify risk factors for both conditions and find interventions in the perioperative period that can impact the occurrence or degree of postoperative delirium (POD) or POCD in older adults. This article is a thorough literature review of the many aspects of these diagnoses and what perioperative providers can do to mitigate the risk of patients developing either of these diagnoses. Available data illustrate important preoperative screening tools for patients at high risk of either of these postoperative complications and discuss various anaesthetic techniques that produce either a significant (cerebral oximetry) or a non-significant (electroencephalogram-monitored anaesthesia and regional anaesthesia) reduction in POD or POCD in patients aged 50 years or older.

**Keywords**

Cerebral oximetry, delirium pathophysiology, delirium risk factors, delirium screening, electroencephalogram (EEG)-guided anaesthesia, general versus regional anaesthesia, postoperative cognitive decline, postoperative delirium, postoperative delirium prevention, propofol versus sevoflurane

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## Article highlights

- Multiple screening tests are available to screen patients for cognitive impairment, and the Confusion Assessment Method is a helpful test to screen for delirium in the immediate postoperative period.
- Medicine reconciliation and identification and removal of potentially inappropriate medications per Beer's list are important tasks that should not be overlooked, especially during a preoperative appointment.
- Intravenous anaesthetics have been shown to decrease the incidence of postoperative delirium when compared with volatile inhalational anaesthetics.
- Adjuncts, such as more than one local anaesthetic nerve block or the use of an epidural during major abdominal or thoracic surgery, decrease the incidence of postoperative delirium, presumably through achieving better postoperative pain control.
- A low baseline cerebral oximetry measurement is an indication that a patient is more likely to develop postoperative cognitive dysfunction. A timely correction (<157 minutes) of intraoperative cerebral oximetry decline is also an important mitigation factor.

Surgical interventions are increasingly being used in older adults as treatment for medical conditions; approximately 38% of all procedures are performed in individuals aged 65 years or older in the USA in 2018 compared to 23% in 2010 in the USA.[1,2] As such, there has been an increasing interest in understanding how surgical and anaesthesia interventions affect the occurrence of postoperative delirium (POD) or postoperative cognitive dysfunction (POCD). The learning objectives of this review include defining delirium and POCD, and identifying the best methods to screen patients at risk. We aim to examine non-pharmacological interventions and different anaesthetic techniques that can potentially decrease postoperative cognitive effects on the elderly.

## Defining delirium

Delirium is an acute impairment in consciousness that represents a change from the patient's baseline cognitive functioning and is not better explained by a preexisting or other neurocognitive process.[3] Delirium should be assumed to have a reversible cause until proven otherwise. POD usually develops over the course of hours to a few days. Symptoms of delirium typically resolve after 1 week or before discharge, although some symptoms may persist longer.[3–5]

A central feature of delirium is the disturbance in attention (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition [*DSM-V*]).[3] This disturbance in attention is often accompanied by a reduced awareness of the environment. As both attention and environmental awareness are essential aspects of normal consciousness, delirium represents an altered state of consciousness.[3]

Delirium can present as different subtypes. The most common presentation (45–55% of patients) is decreased psychomotor activity, with apathy, lethargy and withdrawn behaviour.[6–8] As these patients are often quiet and do not cause a disturbance, these cases of delirium can often be overlooked. In contrast, approximately 20–30% of patients with delirium exhibit increased psychomotor activity, with agitation, refusal to cooperate with medical care and/or mood lability.[9] Individuals with this subtype may demonstrate inappropriate behaviours (i.e. screaming, swearing or incoherent sounds), especially at night and when there is a deficit of environmental cues.[3] Another subtype of delirium is a mixed motor presentation, which occurs in approximately 25–30% of cases and presents with fluctuations between agitation and quiet confusion.[9] Finally, some patients with delirium may exhibit normal psychomotor activity.[10] A disturbance in another area of cognition, such as hallucinations, illusions or alterations in perception, is also required for the diagnosis of delirium. The circadian rhythm is often disrupted in individuals with delirium, leading to disturbances in the sleep–wake cycle.[3] Disturbances may range from insomnia and daytime sleepiness to nighttime agitation or full reversal of the sleep–wake cycle.[3,11]

## Defining postoperative cognitive dysfunction

POCD is not listed as a diagnosis in the *DSM-V*, leading to the development of various definitions and diagnostic criteria.[12] The International Perioperative Cognition Nomenclature Working Group, an expert panel of clinicians and scientists, considers POCD to be a new cognitive impairment (CI) occurring after a surgical procedure that exceeds the anticipated length of time required to fully recover from the acute effects of anaesthesia and surgery.[12] POCD often causes impairment in memory and decreased ability to perform intellectual tasks, although it can also affect orientation, attention, perception, judgement and consciousness.[12] It can arise shortly after surgery, although it may be overshadowed by delirium, pharmacological interventions, immobility or sleep deprivation during the early postoperative period. POCD does not resolve within days or weeks and can last up to 6–12 months.[12]

The exclusion of POCD from the *DSM-V* is because research into perioperative cognitive changes has largely occurred in surgical or hospital settings, separate from generalizable community-based studies on neurocognitive dysfunction and from the professional groups that study it, such as psychiatrists, neurologists, neuropsychologists and geriatric specialists.[13] A recent consensus recommendation by the Nomenclature Consensus Working Group suggests integrating research on POCD into the broader clinical community and consequently incorporating POCD within the diagnostic criteria of neurocognitive disorders currently in the *DSM-V*.[14] Additionally, the same group proposed that the term 'perioperative neurocognitive disorders' be used to describe CIs identified during the perioperative period.[14] This term would be subdivided into the following: (1) neurocognitive disorder, when cognitive decline is diagnosed before surgery; (2) delayed neurocognitive recovery, when the cognitive decline occurs acutely postoperatively (including delirium) but persists only for up to 30 days after surgery; and (3) postoperative neurocognitive disorder, when it lasts up to 12 months or beyond.[13]

## Risk factors for postoperative delirium

There are several well-studied risk factors for POD across multiple types of surgeries: the demographic risk factors most consistently associated with POD are increasing age and preexisting CI.[15] Residency in a nursing facility is another risk factor for delirium.[15] Comorbidities consistently associated with POD are psychiatric disorders (including depression and diagnoses involving psychosis); visual impairment; cerebrovascular diseases, including stroke and other conditions affecting the blood vessels supplying the brain (i.e. carotid stenosis); and end-stage renal disease. When examining risk scores that attempt to quantify comorbidity, increasing American Society of Anesthesiologists class showed a consistent correlation with an increased risk of delirium.[16]

When examining preoperative medication use, multiple studies that examined the effect of preoperative use of psychoactive medications, including antidepressants, narcotics and other psychoactive medicines, on postoperative delirium demonstrated a two- to sevenfold increased risk of POD, although the studies did not report the indications for the medications investigated.[17–19] Regarding perioperative factors, there was evidence that the requirement of intraoperative blood transfusions was a consistent risk factor for delirium, with mixed evidence for intraoperative blood loss and fluid administration.[16]

## Prevalence of postoperative delirium/cognitive dysfunction

The prevalence of POD and POCD in older adults varies based on the population being examined, the cognitive performance tests used for diagnosis and the stringency of methods to define each diagnosis.[20] A recent meta analysis of studies examining older adults in the emergency department determined that the estimated prevalence of delirium was 15%.[21] The prevalence of POD varies by the type of surgery and the associated procedural risk: otolaryngology and general surgery have a lower prevalence at 12–13%, while the prevalence of delirium following major abdominal and cardiac surgery is 50–51%.[22] POD occurred in approximately 16.9% of patients following surgery for a hip fracture.[23] Internationally, delirium occurs in 11–51% of older individuals postoperatively and in up to 81% of older adults in intensive care settings.[20] The reported incidences of POCD have even greater variation due to significantly different methodologies between studies, making data comparison challenging. The incidence of POCD ranges from approximately 20–50% in older patients 3 months after cardiac surgery to 5–55% of patients after major non-cardiac surgeries.[20,24–26] In an observational study of older adults that examined both delirium and POCD, the overall prevalence of POD was 24%.[27] Overall, 47% of patients exhibited POCD at 1 month, although the proportion decreased to 23% at 2 months and 16% at 6 months. Of note, POD significantly increased the risk of POCD at 1 month, but not at 2 or 6 months, and POCD was more common than POD at the 1-, 2- and 6-month evaluations.[27] These findings point to the uncertainty of the relationship between delirium and POCD and whether they share pathophysiology and are part of the same continuum of disorders.

## Preoperative screening to identify patients at risk for postoperative delirium and screening for suspected delirium

Preoperative screening tools can help identify older patients at a higher risk for POD. As preoperative CI increases the risk of POD and other adverse postoperative outcomes, outpatient cognitive assessment tools are a necessary part of perioperative screening in older adults.[28] Tools frequently used include the Mini-Mental Status Examination (MMSE), the Mini-Cog, the Montreal Cognitive Assessment (MoCA) and the Saint Louis University Mental Status Exam (SLUMS).[29–33]

The MMSE is a brief mental status examination to assess global cognitive function.[20] Lower MMSE scores typically indicate the presence of CI, although the range may need to be adjusted to account for the patient's age and education level.[30,34] For older adults undergoing hip fracture repair surgery, a lower MMSE score was significantly associated with the development of POD (20.45 versus 24.61).[35] The MMSE helps predict the risk of POD when used preoperatively to assess CI; however, it requires a fee.[36]

The Mini-Cog is a test that takes less than 5 minutes and asks participants to repeat three words, draw a clock and then recall the three words.[32] It is a screening tool for CI that is not impacted by education level. A Mini-Cog score of <3 is significantly associated with POD.[37] Mini-Cog scores consistent with CI on surgery day are associated with a 12.8 times higher risk of POD, and preoperative clinic visit scores consistent with CI are associated with a 29 times higher risk of POD.[38]

The MoCA is a 10-minute (11-question) free screening tool with scores of 0–30 that assesses visuospatial processing (clock drawing), executive function, memory, language and attention.[31] Lower MoCA scores have been associated with POD.[39]

The SLUMS is an 11-item, 10-minute screening tool scored from 0 to 30.[29] A score of <27 corresponds to CI. The SLUMS is similar in sensitivity to the MMSE for detecting dementia; however, it has a higher sensitivity for detecting mild neurocognitive disorder or impairment.[40] Similar to other tools mentioned, CI, as measured by SLUMS, has been associated with the development of POD.[41] Both the MoCA and the SLUMS include a clock-drawing test, which itself has been shown to predict POD in older patients.[42]

A narrative review that included the Mini-Cog, SLUMS, MoCA and MMSE2 (second edition) found that MoCA has the highest specificity and sensitivity combination for detecting mild CI in older patients.[33] However, the choice of screening tool may also depend on factors such as availability of tools, institutional preference or available time in preoperative appointments. It is important to screen patients using an effective screening tool to identify those at a higher risk for POD, so patients can be informed of their risk and appropriate preventative interventions can be used. Performing a medication reconciliation during the preoperative visit is also important. Polypharmacy and inappropriate medication use commonly affect older adults, and certain medications influence a patient's likelihood of developing POD.[43–45] For example, beta-blockers and benzodiazepines have been associated with an increased risk of POD in patients undergoing vascular and orthopaedic surgery.[19] Psychoactive medications can lead to a higher risk of POD.[43] Examples of psychoactive medications associated with delirium include medications with anticholinergic activity, such as first-generation antihistamines, benzodiazepines, non-benzodiazepine receptor agonist hypnotics (Z drugs), antipsychotics and opioids.[43]

Identifying potentially inappropriate medications (PIMs) can be done using the Beer's criteria, a list of medications maintained by the American Geriatrics Society that should be avoided in older adults.[43] The use of PIMs has been shown to significantly increase the risk of POD in older patients.[46] Familiarizing oneself with a patient's medication list and identifying PIMs are important steps in identifying patients at risk of POD during preoperative evaluation.

If postoperative delirium is suspected in a patient, the Confusion Assessment Method (CAM) is widely used to quickly screen patients for POD.[47] The CAM assesses acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness.[47] To diagnose delirium, acute onset with fluctuating course and inattention must be present along with either disorganized thinking or an altered level of consciousness.[47]

## Non-pharmacological interventions for the prevention and treatment of postoperative delirium in geriatric patients

While pharmacological interventions can be helpful in the prevention of POD, there are several non-pharmacological interventions that can be implemented in the prevention and treatment of POD. Staff education, including information on delirium assessment, prevention and treatment, has been shown to reduce POD.[48] It is important that staff recognize POD, as early recognition of symptoms can help prevent progression.[49] The implementation of a delirium screening tool has been shown to decrease the incidence of POD.[50] Educated staff are often crucial to the implementation of proper interventions. A German study found preventative interventions tailored to patient needs by a delirium prevention team and carried out by staff who received delirium education reduced delirium incidence in those undergoing elective orthopaedic and abdominal surgery.[51] Risk factor screening with subsequent strategies to modify risk can significantly reduce delirium incidence.[52] Effective interventions frequently used in the prevention of POD include sleep promotion (sometimes with the use of eye masks and earplugs), minimizing interruptions by the care team (especially at night), patient reorientation, cognitive stimulation, sensory and physical stimulation, optimization of vision and hearing, maintaining a quiet environment, meal companionship and family involvement.[51–53] Family involvement at the bedside is particularly important in preventing POD as it provides a familiar face to help orient and reassure the patient.[52]

Hydration after surgery is a modifiable risk factor that can influence POD, with long fluid fasting times being associated with POD.[53] Shortening meal fasting time and adequate hydration can decrease POD incidence.[54] Assessing the risks of each patient to determine which prevention strategies to use can help reduce POD incidence.

Preoperative patient education techniques have been proven helpful in reducing the incidence of POD. Patients undergoing coronary artery bypass grafting were shown three short videos prior to surgery that detailed the procedure, postoperative care and first-hand patient experience.[55] These videos decreased the incidence of POD compared with the control group.[55] Preoperative site visits led by a multidisciplinary team 1 week prior to surgery were associated with a decrease in POD incidence, duration and severity.[56] It seems familiarizing patients with information about their surgery and the surgical environment may help prevent POD.

## General versus regional anaesthesia

General anaesthesia (GA) affects the entire body and requires a loss of consciousness, for which anaesthesiologists must maintain the patient's airway throughout the surgical procedure.[57] In contrast, regional anaesthesia (RA) is the loss of sensation to a specific part of the body, while consciousness remains intact, and thus a patient can maintain their own airway.[58]

Examples of RA include spinal anaesthesia, epidurals, a caudal block or various nerve blocks.[58] It seems logical that using RA could reduce the incidence of POD or POCD in older patients (>65 years old) undergoing surgeries suitable for RA, most notably orthopaedic surgeries. However, a meta-analysis by Bhushan et al. found that in 3,555 patients aged 65 years or older undergoing hip fracture surgery, there was no difference in the incidence of POD/POCD between the GA and RA groups at 24 hours, 3 and 7 days postoperatively.[59] The Regional Anesthesia vs General Anesthesia (RAGA; ClinicalTrials.gov Identifier: NCT02213380) randomized trial also found that RA – a spinal, epidural or both without sedation – was not superior to GA in patients aged 65 years or older undergoing hip fracture surgery.[60] The RAGA trial was a randomized, multicentre trial of 950 patients, aged 65 years and older, requiring hip fracture repair surgery under either RA or GA. The primary outcome was the incidence of POCD on postoperative day 7.[60] Secondary outcomes included length of stay in the hospital; all-cause 30-day mortality; and delirium severity, duration and subtype. Neither of the outcomes was found to be statistically significant.

However, a study by Gu et al. found that multiple local nerve blocks (fascia iliaca compartment block + sacral plexus block + superior cluneal nerve block) led to lower rates of early moderate delirium and moderate delirium and decreased intraoperative pain threshold index scores compared with the GA group; the intravenous (IV) sufentanil, a potent opioid, dose in the RA group was half that of the GA group.[61]

Combined epidural anaesthesia–general anaesthesia could be another effective alternative to general anaesthesia for older patients undergoing major non-cardiac thoracic or abdominal surgery (>2 hours). Li et al. found that out of 1,720 patients randomly assigned to combined epidural anaesthesia–GA, delirium was significantly less common in the combined group ($p<0.001$).[60] The proposed mechanism is that epidurals decrease the amount of inhalational anaesthetic and improve postoperative analgesia.

## Intravenous versus volatile anaesthetics

Total intravenous anaesthesia (TIVA) uses IV agents for induction and maintenance of anaesthesia, and the most common agent is propofol.[62] Inhalational agents are volatile gases, most commonly sevoflurane. Several studies have compared the effects of propofol-versus sevoflurane-based anaesthesia in elderly patients.[63] Zhang et al. sought to investigate whether one anaesthetic modality (propofol versus sevoflurane) was superior regarding neurocognitive recovery in elderly patients undergoing major cancer surgery (>2 hours) at 14 medical centres in China.[63] A total of 372 patients were randomized and their results were analysed, producing data that favoured propofol in postoperative neuro recovery – the incidence of delayed neurocognitive recovery was 14.8% with propofol versus 23.2% with sevoflurane (odds ratio: 0.577; 95% confidence interval: 0.342–0.975, $p=0.038$).[63] The propofol group also reported superior pain control on postoperative days 1 and 2 ($p=0.013$ and 0.015, respectively).[63] These authors also published a follow-up to their randomized controlled trial (RCT), which did not find a significant difference in long-term survival between the propofol group and the sevoflurane group ($p=0.834$).[64]

Geng et al. also found propofol favourable to sevoflurane or isoflurane for reducing cognitive dysfunction following laparoscopic cholecystectomies in elderly patients on postoperative days 1 and 3, respectively (propofol versus isoflurane, $p<0.001$; propofol versus sevoflurane, $p=0.013$).[65]

Other studies have corroborated the findings by Zhang et al. and Geng et al., including a nationwide population-based study in Japan that favoured TIVA as an inhalational anaesthetic for decreasing POD and complications in older patients.[63,65,66]

## Cerebral oximetry and electroencephalogram-guided anaesthesia

Near-infrared spectroscopy (NIRS) is a non-invasive technology that can continually measure tissue oxygenation.[67] NIRS technology exploits the fact that oxygenated and deoxygenated haemoglobin differ in their absorption patterns, causing the light spectrum to change based on the level of oxygenation it detects. The brain tissue most frequently monitored is the frontal lobe, which is sensitive to hypoxic and hypotensive episodes. Continuous monitoring of changes in cerebral regional oxygen saturation ($rSO_2$) allows for rapid treatment to mitigate potential psycho-neurological outcomes of patients undergoing these surgeries.

Kim et al. specifically looked at the incidence of POCD in 87 patients older than 65 years undergoing lumbar spinal surgery in the prone position with intraoperative monitoring of $rSO_2$.[68] All patients underwent the Korean MMSE the night prior to surgery and again on their seventh postoperative day. A Bispectral Index (BIS) was used to monitor the depth of anaesthesia, and sevoflurane was titrated to achieve a BIS between 40 and 60 for all patients. Two NIRS monitors were placed on the patient's forehead; the anaesthesiologists were blinded to $rSO_2$ data that were recorded at 30-second intervals during the surgery. Their results found that a duration of greater than 157 minutes of cerebral $rSO_2$ <60% of a patient's baseline was the only independent risk factor for POCD on postoperative day 7.[68] Demographics, the length of anaesthesia, the amount of pressors used, the need for transfusion, baseline $rSO_2$ values and the patient's postoperative pain score were similar between patients who developed POCD and those who did not. However, the intraoperative $rSO_2$ values were significantly lower for the POCD group compared with the non-POCD group (51 ± 10% versus 56 ± 8%, $p=0.025$), and the duration of $rSO_2$ <60% for >157 minutes of a patient's baseline was also longer in the POCD group ($p=0.019$).[68]

NIRS has shown to be a more useful tool for estimating the POCD risk in older patients undergoing surgery than electroencephalogram (EEG)-guided anaesthesia. The ENGAGES study (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes Study; ClinicalTrials.gov Identifier: NCT02241655) in 2019 did not find any convincing evidence to use EEG-guided anaesthesia to decrease POD in older adults (median age: 69 years) undergoing major surgery.[69] Specifically, the study aimed to limit EEG burst suppression, which can signify GA and hypoxic–ischaemic injury. Even though the control group experienced a statistically significant increased duration of EEG suppression (13 minutes) compared with the guided group (6 minutes), this did not lead to a difference in POD rates between the two groups.

Wildes et al. conducted a randomized EEG study on 1,232 patients aged 60 years or older undergoing major surgery with GA.[69] Patients were randomized in a 1:1 manner. The primary outcome of POD occurred in 26% of the EEG-guided group and 23% in the usual care group (95% confidence interval: -2 to 8%, $p=0.22$).[69] Therefore, they did not recommend EEG monitoring as an adjunct for reducing the risk of POD in elderly patients undergoing major surgery.

Schoen et al. hypothesized that correcting low preoperative $rSO_2$ would decrease the incidence of POD after on-pump cardiac surgery.[70] Their hypothesis was not supported by their data. The researchers conducted an observational study (n=256) and recorded each patient's preoperative $rSO_2$ using the INVOS Cerebral Oximeter 5100 (Somanetics, Troy, MI, USA) with a bi-hemispherical NIRS sensor. If the patient was found to have a low $rSO_2$ the day prior to surgery, the patient was supplied with 4 L/min of supplemental oxygen until their peripheral arterial oxygen saturation was greater than 98%, at which point their $rSO_2$ was rechecked to assess their compensation of hypoxaemia. It was found that 62 patients (26.8%) developed POD: 45 patients developed POD on postoperative day 1 (25.8%), 16 patients developed POD on postoperative day 2 (25.8%) and one patient developed POD on postoperative day 3 (1.6%).[70] POD was diagnosed using the CAM-intensive care unit screening test. Interestingly, relative changes in $rSO_2$ – baseline value versus minimal intraoperative $rSO_2$ value or area under the curve differences – did not differ between patients who did or did not develop POD. The absolute values, however, did differ and were predictors of delirium. Thus, a lower preoperative $rSO_2$ value was found to be an independent risk factor for developing POD, regardless of the intraoperative cerebral oximetry course.[70] Overall, Schoen et al. reiterated a common finding among similar studies: the patients who develop POD after cardiac surgery are more ill and have a lower cognitive capacity compared with those patients who do not develop POD.[71–73]

## Conclusion

The USA is approaching a time when the elderly will outnumber children.[6] As the older population grows, so do the rates of dementia.[74] Surgeries are known to be associated with POD and POCD in older adults – up to 50% in certain populations.[20,22–26] With an increase in the number of older adults and the high prevalence of POD and POCD in patients undergoing surgery, it is important to understand these outcomes and how to prevent them.

Risk factors include advanced age, visual/hearing impairment, cerebrovascular disease, end-stage renal disease and, most importantly, preexisting CI.[15,16] Tools such as the MMSE, SLUMS, MoCA and Mini-Cog can be used to screen for CI preoperatively.[29–33] Scores consistent with CI on each of these screeners are associated with delirium.[35,37–39,41] Additionally, all medications a patient is taking should be reviewed before surgery; the Beer's list is a useful tool in identifying medications to avoid in patients both pre- and postoperatively.[43–45] Non-pharmacological preventative measures have been well-researched and are widely used to help prevent POD. Most are interventions implemented in the postoperative period, such as patient re-orientation, optimizing vision and hearing, optimizing sleep, maintaining a quiet environment and family involvement.[51–53]

There has been an emerging interest in perioperative anaesthetic interventions to decrease POD and POCD. Specific anaesthetic agents may reduce unwanted cognitive side effects following surgery, with IV infusions favoured over inhalational gases.[63,65] For major abdominal or non-cardiac thoracic surgery, epidurals as adjuncts to GA decrease the incidence of POD, most likely from better pain control and thus decreased opioid usage in the postoperative period.[60]

Patients undergoing hip replacement surgery may benefit from multiple local anaesthetic blocks to reduce the incidence of POD in the same vein – better pain control and fewer opioids.[61]

Cerebral oximetry during the perioperative period is an effective tool for anticipating POD and POCD, whereas EEG monitoring is not.[68,69] A lower preoperative $rSO_2$ value confirmed that cerebral oximetry is an effective tool for predicting which patients may develop postoperative cognitive decline.[75,76] Overall, the data suggest that monitoring cerebral oxygenation and intervening preoperatively bode well for cognitive outcomes postoperatively in older patients undergoing surgery and represent a developing area of research.[70] ❑


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