Review Article

Postoperative cognitive recovery and prevention of postoperative cognitive complications in the elderly patient

ABSTRACT

Elderly patients undergoing surgery are at higher risk of life-altering and costly complications. This challenge is increasingly recognized with the growing geriatric surgical population. Advanced age and comorbid conditions, such as disability and frailty that often develop with age, are all independent risk factors of postoperative morbidity and mortality. A common factor in this age group is cognitive impairment, which poses a challenge for the patient and clinician in the perioperative setting. It affects the capacity for informed consent and limits optimization before surgery; furthermore, an existing impairment may progress in severity during the perioperative period, and new onset of signs of delirium or postoperative cognitive dysfunction may arise during postoperative recovery. In this article, we aim to review the current literature examining the latest definitions, diagnostic criteria, and preventive strategies that may ameliorate postoperative cognitive complications.

Key words: Neurocognitive recovery, postoperative cognitive dysfunction, postoperative neurocognitive disorders

Introduction

Savage GH, first recognized the phenomenon of postoperative cognitive impairment in his publication in the British Medical Journal titled "*Insanity following the Use of anesthetics in operations*" in 1887, which described "*a series of cases of insanity in which the use of anesthetics, in predisposed subjects, has been followed by insanity*."[1] Savage's publication is considered a milestone of the early efforts to understand the effects of anesthesia and surgery on cognition.

Postoperative delirium (POD) is a common occurrence in the post-anesthesia care unit, making it far more clinically recognizable than postoperative cognitive dysfunction (POCD), which has a more indolent and subtle course long after the proposed effect of the anesthetic agent has dissipated. Therefore, it is imperative to counsel the patient on the impact of anesthesia and surgery on their med- to long-term cognitive abilities.

However, over a century since Savage's first accounts of postoperative cognitive impairment, there remains much confusion surrounding POCD in the literature, from varying methodology, ill-defined criteria, and lack of control groups in most of the studies.

Access this article online	
Website: https://journals.lww.com/sjan	Quick Response Code
DOI: 10.4103/sja.sja_529_23	

How to cite this article: Almuzayyen HA, Chowdhury T, Alghamdi AS. Postoperative cognitive recovery and prevention of postoperative cognitive complications in the elderly patient. Saudi J Anaesth 2023;17:550-6.

Hisham A. Almuzayyen[1,2], Tumul Chowdhury[3], Abdulkareem S. Alghamdi[1]

[1]Department of Anesthesiology, Johns Hopkins Aramco Healthcare, Dhahran, [2]King Fahad Hospital of University, Imam Abdulrahman Bin Faisal University, Khobar, Saudi Arabia, [3]Department of Anesthesia, Toronto Western Hospital, Clinical Investigator, UHN, University of Toronto, Toronto, Canada

Address for correspondence: Dr. Hisham A. Almuzayyen, Address: EDSB7287, P.O. 32272, Saudi Arabia.
E-mail: HAmuzayyen@iau.edu.sa

Received: 16-Jun-2023, **Revised:** 25-Jun-2023, **Accepted:** 26-Jun-2023, **Published:** 18-Aug-2023

Postoperative Cognitive Disorders

Neurocognitive impairment after surgery may present as any of the following.

1. A progression of an existing neurocognitive disorder
2. New onset delirium
3. POCD

The diagnostic and statistical manual of mental disorders (DSM-5) has amended its criteria for the diagnosis of neurocognitive disorders, which may be reported by a patient, informant, or tested by a clinician.[2]

- Mild neurocognitive dysfunction: the decline of cognitive function, requiring adjustments to maintain independence in activities of daily living that extend beyond the normal changes of aging.
- Major neurocognitive dysfunction: significant burden of cognitive impairment that results in impaired activities of daily living.

The DSM-5 outlines seven domains to be evaluated in neurocognitive dysfunction:

1. Learning and memory: the ability to learn and recall new information.
2. Language: Comprehension or expression
3. Perceptual motor: Visual perception and coordination
4. Social cognition: Insight and recognition of emotions
5. Complex attention: Sustained, divided, or selective attention and speed of processing.
6. Executive function: Planning, decision-making, and flexibility
7. Delirium: An acute fluctuating level of disturbance in attention, awareness, and cognition developed in a short period.

The DSM-5 does not currently define POCD; however, it is commonly described in the literature as a postoperative decline in cognitive function lasting months to years after surgery.

Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction is a transient decline of patients' cognitive abilities from their baseline in the days shortly after surgery. In a study where they followed 336 elderly patients undergoing major non-cardiac surgery under general anesthesia and assessed for POCD at 7,98,532 days postoperatively, the prevalence of persistent POCD was 0.9% for 1–2 years after the operation.[3] Cognitive decline may be noted in any of the seven domains outlined in the DSM-5. Patients may experience difficulties writing, managing money, or remembering lists; this can significantly impact their life after discharge home. In a study of a patient with hip fractures, those who developed POCD had struggled to function socially and had difficulties in activities of daily living at one year.[4] A study that followed up on 700 patients for eight years found that POCD at one week was associated with prematurely leaving the job market and dependency on social payments.[5] Furthermore, POCD increases mortality risk one year after surgery.[5] An 11-year follow-up after surgery has shown no association between POCD and dementia.[6]

The incidence of POCD in the elderly one week after surgery is around 30% and decreases to 10% and 1% at three months and one year, respectively, owing to the reversibility of the disease.[6–8] All previously cited data are from patients undergoing major non-cardiac surgery; neurocognitive complications are well-documented in cardiac surgery with cardiopulmonary bypass established as an independent risk factor for postoperative cognitive decline.[9] Although POCD may affect patients of all age groups, elderly patients are at increased risk of developing cognitive decline after surgery.

Controversies Surrounding the Validity of POCD

Several well-designed studies have compared the prevalence of cognitive decline between age-matched surgical and non-surgical groups, in the study done by the International Study of Post-operative Cognitive Dysfunction (ISPOCD), it was found that POCD occurred in 25.8% at one week after surgery and 9.9% at three months, compared to 3.5% and 2.8% in the control group at one week and three months, respectively.[8] Another study showed a comparative cognitive decline in the elderly similar to POCD, irrespective of surgery or significant illness.[10] The findings of the authors make us question the existence of POCD; the authors highlight that prior studies' conclusions were based on age-matched groups alone, where surgical patients are more prone to comorbid illness evidenced by the need for surgery, which introduced a bias for the diagnosis of POCD, comparing elderly patients undergoing surgery with an acutely ill age-matched group yielded no difference in cognitive decline. There lies a challenge for future research to clarify the phenomenon of POCD; there is a need for large prospective trials matching the surgical groups to diseased matched control groups to confirm or deny the existence of such a cognitive disease.

Another topic of controversy is the clinical tools used to diagnose POCD. For accurate detection of the subtle and specific neurocognitive changes, diagnosis of POCD should include a battery of tests that span the cognitive domains described by the DSM-5. Most current research has used the Mini-Mental State Examination (MMSE) as a tool for the assessment of POCD. This brief and accessible test was

designed for dementia screening and is too crude to identify the subtle features of cognitive decline associated with POCD. There are various options for sensitive neuropychometric testing, such as the Montreal Cognitive Assessment Tool, Addenbrooke's mental examination III, and the Quick Mild Cognitive Impairment screen.[11]

Proposal for New Definitions

Until the time being, POCD is not an official psychiatric diagnosis. The international perioperative cognition nomenclature working group has addressed this through a discussion of an expert panel, which recently proposed a new narrative for describing perioperative cognitive disorders.[12] The aim is to align the diagnostic criteria of POCD with neurocognitive disorders defined by the DSM-5 in the general population.

Recommendations for perioperative neurocognitive disorders

The term "perioperative neurocognitive disorders" (NCD) can be used as an umbrella term for cognitive impairment and/or change identified during the perioperative period. This includes cognitive impairment identified before the procedure, any form of acute events (such as delirium), cognitive decline diagnosed up to 30 days after the procedure (described as delayed neurocognitive recovery), or up to 12 months (postoperative neurocognitive disorder).

Recommendations for pre-existing cognitive impairment

Pre-existing cognitive impairment is the term used to describe patients with objectively measurable subtle cognitive impairment at baseline.

Recommendations for postoperative delirium

Postoperative delirium is defined as delirium, which occurs in the hospital up to one-week post-procedure or until discharge (whichever occurs first) and meets DSM-5 diagnostic criteria. Factors to consider when diagnosing POD.

- Unmasked pre-existing vulnerabilities like drug/alcohol withdrawal, dementia, history of delirium.
- Persistent drug effect
- Other physiological derangements (metabolic abnormality, hypoxia, infection electrolyte imbalance)
- Lucid intervals (not mandatory, but should be documented)

Recommendations for postoperative cognitive disorders

A battery of neuropsychometric tests ideally measures the newly named postoperative NCD. A reduction of 1–2 standard deviation (SD) defines mild postoperative NCD, and >2 SD defines major postoperative NCD, in alignment with the definition of general population NCD diagnosis criteria in the DSM-5. The working group does not recommend which neuropychometric test to use or which cognitive domains to test. It directs clinicians away from early testing for POCD (<7 days), emphasizing the resolution of the acute effects of surgery and anesthetic before diagnosing cognitive impairment. The efforts made by the working group are valuable, and it is the responsibility of the broader medical community to embrace change that advances consistency in diagnosing POCD.

Risk factors for developing POCD are identified to be advanced age, lower educational level, and history of a cerebral vascular accident. Both preoperative major cognitive disorder and cognitive dysfunction at discharge correlate with POCD three months after surgery.[4,13,14] Other studies have suggested other predictors for early POCD, including duration of anesthesia, postoperative infections, redo surgeries, and postoperative respiratory complications.[8]

The pathogenesis of POCD remains unknown, with much research focusing on the role of neuronal death, neuroinflammation, and microemboli in the cerebral vasculature. Animal studies have shown that inhalational anesthetic agents potentiate neuronal death through the degradation of the cholinergic system by amyloid plaques and neurofibrillary tangles.[11,13] Cholinergic pathways play a crucial role in consciousness, learning, and memory. Inhalational anesthetic agents increase the permeability of the endothelial cells in the cerebral vasculature allowing entry of cytokines that result in neuroinflammation and neuronal tissue damage.[15] Microemboli from the surgical site or air entrainment may cause micro cerebral infarcts and have been studied using magnetic resonance imaging (MRI), but no clear correlation was found.[11] Multiple imaging studies have been conducted to identify the structural brain alterations related to POCD. A systematic review of 10 MRI studies showed weak evidence suggesting a correlation between POCD with reduced thalamic volume, reduced hippocampal volume, white matter pathology, and reduced cerebral blood flow compared to healthy controls.[16]

European Society of Anesthesiology Guideline on Postoperative Delirium

The European Society of Anesthesiology published, in 2017, an evidence-based and consensus guideline aiming for the prevention and treatment of POD.[17] The cornerstone of the guidelines was the preoperative identification of patients at higher risk of developing POD, of which elderly patients are recognized as an at-risk group with reduced tolerance to major physiological stress such as surgery.

Table 1: ESA statement regarding the prevention and treatment of POD

Statement	Age group		Grade of evidence
	All adults	>65 years	
They suggest implementing fast-track surgery to prevent POD	[18–19]	[18,20]	B
They suggest avoiding routine premedication with benzodiazepines except for patients with severe anxiety		[21–27]	B
They recommend monitoring the depth of anesthesia	[28–30]	[22,31]	A
They recommend adequate pain assessment and treatment	[31]	[25,28,32–34]	A
They suggest using a continuous intraoperative analgesia (e.g., with remifentanil infusion)	[35,36]		B
They recommend promptly diagnosing POD, establishing a differential diagnosis, and instituting treatment	[37]	[38–40]	A
They suggest using low-dose haloperidol or low-dose atypical neuroleptics to treat POD	[40,41]	[42,43]	B

Table 1 summarizes the European Society of Anesthesiology statement regarding the prevention and treatment of POD. Further recommendations regarding elderly patients emphasized non-pharmacological measures in preventing and treating POD, involving orientation (clock, sunlight, communication, etc.), visual/hearing aids, noise reduction, maintenance of day/night rhythm, avoidance of unnecessary indwelling catheters, early mobilization, and early nutrition.

Prevention of Perioperative Neurocognitive Disorders

Prevention is the most critical aspect of the management of perioperative NCDs. In the following, we aim to review the available evidence for preventive strategies to mitigate the development of perioperative NCDs.

Type of Anesthesia

The etiology of POCD, as referenced earlier, is believed to be due to neuroinflammation leading to cholinergic dysfunction and synaptic impairment. Therefore, many believe that regional anesthesia may limit the incidence of POCD; however, current research has failed to confirm that belief.

A 2022 systematic review and metanalysis of 8 randomized controlled trial (RCTs) that included 3555 elderly patients undergoing hip fracture surgery under general vs. regional anesthesia showed no significant difference in the incidence of postoperative dysfunction at 24h, 3 days, and 7 days, respectively.[44]

The authors emphasized the heterogeneity of the primary RCTs in defining and diagnosing POCD, a reoccurring challenge for research concerning postoperative cognitive decline. A 2018 Cochrane review reported low-certainty evidence that maintenance with propofol-based total intravenous anesthesia (TIVA) may reduce POCD (odds ratio 0.52; 95% confidence interval [CI] 0.31–0.87; 869 participants).[45] Starting from 3215 eligible patients, the analysis was hampered due to vast heterogeneity in methodology, emphasizing the need for consistency in defining POCD. A more extensive 2021 systematic review and meta-analysis of 15 RCTs comparing propofol vs. inhalational maintenance of anesthesia of 1854 elderly patients undergoing noncardiac surgery showed low-quality evidence of the superiority of propofol maintenance in the prevention of POCD.[46]

This effect is more likely linked to using electroencephalogram (EEG) guidance for the depth of anesthesia, often coupled with propofol maintenance, into which a considerable amount of research exists.

Another Cochrane systematic review has highlighted that optimization of anesthetic depth guided by processed EEG indices and auditory evoked potential could reduce the risk of POD at 3 months postoperatively in patients ages 60 years and over with moderate quality evidence.[47] The Cognitive Dysfunction after Anesthesia Trial has demonstrated that POCD can be prevented in 23 patients for every 1000 patients undergoing noncardiac surgery at three months postoperatively using a bispectral index -guided optimization of anesthetic depth and 83 patients for every 1000 for POD.[29] The impact of POCD in one week and one year remains uncertain.

Conversely, a meta-analysis of four randomized controlled trials showed no correlation between anesthetic depth and the development of POCD.[48]

Anesthetic Adjuncts

Dexmedetomidine, the central alpha-2 adrenoreceptor agonist is recognized as a neuroprotective sedative and is considered to decrease the incidence of perioperative delirium. Dexmedetomidine acts on the locus coeruleus, causing sedation, opioid-sparing analgesia, and imitates physiologic sleep without causing respiratory depression. Possible mechanisms for the ability of dexmedetomidine to reduce postoperative cognitive dysfunction include inhibition of neuroinflammation, analgesia, and central nervous system protection.[49] In a meta-analysis of seven randomized

controlled trials that used dexmedetomidine as an adjunct to general anesthesia, POCD at day seven was significantly lower in the treatment group (R = 0.34%; 95% CI 0.19–0.61; $P < 0.001$).[50]

The RCTs studied assessed cognition with postoperative MMSE without a baseline cognitive assessment which weakens the certainty of the association of dexmedetomidine and POCD prevention.

Ketamine is an N-methyl-D-aspartate antagonist with anesthetic and analgesic properties and has been shown to exhibit neuroprotective effects. In a systemic review and metanalysis of 6 trials comparing intraoperative administration of ketamine vs. no intervention, only 3 out of the 6 trials showed a lower risk of developing POCD in the intervention arm (163 patients, RR 0.34, 95% CI [0.15–0.73]), however, the analysis presented many limitations, and the quality of evidence for ketamine in the prevention of POCD is deemed very low.[25,51]

Postoperative cognitive dysfunction is correlated to high concentrations of inflammatory markers such as C-reactive protein and interleukin-6 in peripheral circulation and cerebrospinal fluid.[52] Therefore, glucocorticoids were studied to evaluate their impact on POCD. A meta-analysis of 5 RCT showed no significant difference between the dexamethasone and placebo groups in terms of incidence of POCD at 30 days after surgery.[53] An anti-inflammatory agent, parecoxib, a selective cyclooxygenase-2 inhibitor, has been shown in preclinical studies to reduce levels of neuroinflammatory mediators S100 calcium-binding protein b (S100B), and neuro-specific enolase, which has been clinically correlated with POCD.[54]

A meta-analysis of 4 RCTs of 900 patients showed that parecoxib was effective in POCD at 7 days incidence with reduced levels of S100B and IL-6, but the strength of the conclusions is limited by 3 out of 4 using MMSE for neurocognitive assessment.[55]

In conclusion, as POCD becomes a better-known, well-defined clinical entity, anesthesiologists will be better informed for a transparent discussion with patients during consent preoperatively. One in 10 elderly patients above 65 years of age will suffer from POCD at 3 months postoperatively; the risk of developing a reduced quality of life may outweigh the benefits of surgery for some patients. One of the recent advances in the study of POCD is the working group proposal for a quantified measure of cognitive decline for the diagnosis of POCD. They also emphasize the importance of timing cognitive assessment and avoiding premature testing, which confuses the late complication of POCD with the acute effects of surgery and anesthesia. There remains a paucity of validated neuropsychometric assessment tools for the cognitive domains that define POCD quantitively. Anesthetic strategies that show promise in reducing the incidence of POCD include propofol TIVA, EEG-guided depth of anesthesia, and dexmedetomidine, with weak evidence supporting the use of ketamine.

By improving our methodology of studying POCD in terms of concise definition and quantifiable assessment tools, there will be stronger evidence of which anesthetic strategies give our patients the best outcome in improving their quality of life after surgery.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Savage GH. Insanity following the use of anaesthetics in operations. BMJ 1887;2:1199-200.
2. Association AP, Association AP, Force APAssociationD 5 T. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013.
3. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, *et al*. Cognitive dysfunction 1–2 years after non-cardiac surgery in the elderly. Acta Anaesthesiol Scand 2000;44:1246-51.
4. Gruber-Baldini AL, Zimmerman S, Morrison RS, Grattan LM, Hebel JR, Dolan MM, *et al*. Cognitive impairment in hip fracture patients: Timing of detection and longitudinal follow-up. J Am Geriatr Soc 2003;51:1227-36.
5. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009;110:548-55.
6. Steinmetz J, Siersma V, Kessing L V, Rasmussen LS. Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study. Br J Anaesth 2013;110:i92-7. doi: 10.1093/bja/aes466.
7. Paredes S, Cortínez L, Contreras V, Silbert B. Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: A qualitative systematic review. Acta Anaesthesiol Scand 2016;60:1043-58.
8. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, *et al*. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998;351:857-61.
9. Sun JH, Wu XY, Wang WJ, Jin LL. Cognitive dysfunction after off-pump versus on-pump coronary artery bypass surgery: A meta-analysis. J Int Med Res 2012;40:852-8.
10. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, *et al*. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology 2009;111:964-70.
11. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: What we need to know and do. Br J Anaesth 2017;119:i115-25. doi: 10.1093/bja/ae×354.
12. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, *et al*. Recommendations for the nomenclature of

cognitive change associated with anaesthesia and surgery—2018. Anesthesiology 2018;129:872-9.
13. Monk TG, Price CC. Postoperative cognitive disorders. Curr Opin Crit Care 2011;17:376-81.
14. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, *et al*. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. Anesthesiology 2015;122:1224-34.
15. Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X. Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: The influence of anesthetic technique, cerebral injury and systemic inflammation. BMC Anesthesiol 2015;15:154. doi: 10.1186/s12871-015-0130-9.
16. Huang C, Mårtensson J, Gögenur I, Asghar MS. Exploring postoperative cognitive dysfunction and delirium in noncardiac surgery using MRI: A systematic review. Neural Plast 2018;2018:1281657. doi: 10.1155/2018/1281657.
17. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, *et al*. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol 2017;34:192-214.
18. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, *et al*. Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. Langenbecks Arch Surg 2014;399:77-84.
19. Pedersen SJ, Borgbjerg FM, Schousboe B, Pedersen BD, Jørgensen HL, Duus BR, *et al*. A comprehensive hip fracture program reduces complication rates and mortality. J Am Geriatr Soc 2008;56:1831-8. doi: 10.1111/j. 1532-5415.2008.01945.x.
20. Larsson G, Holgers KM. Fast-track care for patients with suspected hip fracture. Injury 2011;42:1257-61.
21. Do TD, Lemogne C, Journois D, Safran D, Consoli SM. Low social support is associated with an increased risk of postoperative delirium. J Clin Anesth 2012;24:126-32.
22. Postoperative delirium in older adults: Best practice statement from the American Geriatrics Society. J Am Coll Surg 2015;220:136-48.e1.
23. Nandi S, Harvey WF, Saillant J, Kazakin A, Talmo C, Bono J. Pharmacologic risk factors for post-operative delirium in total joint arthroplasty patients: A case-control study. J Arthroplasty 2014;29:268-71.
24. Milstein A, Pollack A, Kleinman G, Barak Y. Confusion/delirium following cataract surgery: An incidence study of 1-year duration. Int Psychogeriatr 2002;14:301-6.
25. Davies EA, O'Mahony MS. Adverse drug reactions in special populations-The elderly. Br J Clin Pharmacol 2015;80:796-807.
26. Panitchote A, Tangvoraphonkchai K, Suebsoh N, Eamma W, Chanthonglarng B, Tiamkao S, *et al*. Under-recognition of delirium in older adults by nurses in the intensive care unit setting. Aging Clin Exp Res 2015;27:735-40.
27. Taipale PG, Ratner PA, Galdas PM, Jillings C, Manning D, Fernandes C, *et al*. The association between nurse-administered midazolam following cardiac surgery and incident delirium: An observational study. Int J Nurs Stud 2012;49:1064-73.
28. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013;110(Suppl 1):i98-105. doi: 10.1093/BJA/AET055.
29. Chan MTV, Cheng BCP, Lee TMC, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25:33-42.
30. Whitlock EL, Torres BA, Lin N, Helsten DL, Nadelson MR, Mashour GA, *et al*. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. Anesth Analg 2014;118:809-17.
31. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, *et al*. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc 2010;85:18-26.
32. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, *et al*. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003;58:76-81.
33. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: A randomized placebo-controlled study. J Orthop Traumatol 2009;10:127-33.
34. Kurbegovic S, Andersen J, Krenk L, Kehlet H. Delirium in fast-track colonic surgery. Langenbecks Arch Surg 2015;400:513-6.
35. Radtke FM, Franck M, MacGuill M, Seeling M, Lütz A, Westhoff S, *et al*. Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. Eur J Anaesthesiol 2010;27:411-6.
36. Radtke FM, Franck M, Lorenz M, Luetz A, Heymann A, Wernecke KD, *et al*. Remifentanil reduces the incidence of post-operative delirium. J Int Med Res 2010;38:1225-32.
37. Heymann A, Radtke F, Schiemann A, Lütz A, MacGuill M, Wernecke KD, *et al*. Delayed treatment of delirium increases mortality rate in intensive care unit patients. J Int Med Res 2010;38:1584-95.
38. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180:1092-7.
39. Neufeld KJ, Leoutsakos JMS, Sieber FE, Wanamaker BL, Gibson Chambers JJ, Rao V, *et al*. Outcomes of early delirium diagnosis after general anesthesia in the elderly. Anesth Analg 2013;117:471-8.
40. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, *et al*. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009;144:961-9.
41. Montes DM. Postoperative delirium in head and neck cancer patients: A survey of oncologic oral and maxillofacial surgeon practices. J Oral Maxillofac Surg 2014;72:2591-600.
42. Yoon HJ, Park KM, Choi WJ, Choi SH, Park JY, Kim JJ, *et al*. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. BMC Psychiatry 2013;13:240. doi: 10.1186/1471-244X-13-240.
43. Hatta K, Kishi Y, Wada K, Odawara T, Takeuchi T, Shiganami T, *et al*. Antipsychotics for delirium in the general hospital setting in consecutive 2453 inpatients: A prospective observational study. Int J Geriatr Psychiatry 2014;29:253-62.
44. Bhushan S, Huang X, Duan Y, Xiao Z. The impact of regional versus general anesthesia on postoperative neurocognitive outcomes in elderly patients undergoing hip fracture surgery: A systematic review and meta-analysis. Int J Surg 2022;105:106854. doi: 10.1016/j.ijsu.2022.106854.
45. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, *et al*. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev 2018;2018. doi: 10.1002/14651858.CD012317.pub2.
46. Pang QY, Duan LP, Jiang Y, Liu HL. Effects of inhalation and propofol anaesthesia on postoperative cognitive dysfunction in elderly noncardiac surgical patients: A systematic review and meta-analysis. Medicine 2021;100:e27668. doi: 10.1097/MD.0000000000027668.
47. Punjasawadwong Y, Chau-in W, Laopaiboon M, Punjasawadwong S, Pin-on P. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. Cochrane Database Syst Rev 2018;2018:CD011283. doi: 10.1002/14651858.CD011283.pub2.

48. Lu X, Jin X, Yang S, Xia Y. The correlation of the depth of anesthesia and postoperative cognitive impairment: A meta-analysis based on randomized controlled trials. J Clin Anesth 2018;45:55-9.
49. Qiu Z, Lu P, Wang K, Zhao X, Li Q, Wen J, *et al*. Dexmedetomidine Inhibits Neuroinflammation by Altering Microglial M1/M2 Polarization Through MAPK/ERK Pathway. Neurochem Res 2020;45:345-53.
50. Yang W, Kong LS, Zhu XX, Wang RX, Liu Y, Chen LR. Effect of dexmedetomidine on postoperative cognitive dysfunction and inflammation in patients after general anaesthesia: A PRISMA-compliant systematic review and meta-analysis. Medicine 2019;98:e15383. doi: 10.1097/MD.0000000000015383.
51. Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis. Acta Anaesthesiol Scand 2018;62:1182-93.
52. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One 2018;13:e0195659. doi: 10.1371/journal.pone. 0195659.
53. Li LQ, Wang C, Fang MD, Xu HY, Lu HL, Zhang HZ. Effects of dexamethasone on post-operative cognitive dysfunction and delirium in adults following general anaesthesia: A meta-analysis of randomised controlled trials. BMC Anesthesiol 2019;19:113.
54. He X, Wen LJ, Cui C, Li DR, Teng JF. The significance of S100β protein on postoperative cognitive dysfunction in patients who underwent single valve replacement surgery under general anesthesia. Eur Rev Med Pharmacol Sci 2017;21:2192-8.
55. Huang S, Hu H, Cai YH, Hua F. Effect of parecoxib in the treatment of postoperative cognitive dysfunction: A systematic review and meta-analysis. Medicine 2019;98:e13812. doi: 10.1097/MD.0000000000013812.