Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2018137971
2018;21 (1):87-99

- Gözde İNAN[1]
- Zerrin ÖZKÖSE ŞATIRLAR[1]

REVIEW ARTICLE

A CLINICAL REVIEW OF THE CONSEQUENCES OF ANESTHESIA AND SURGERY IN THE ELDERLY BRAIN: "THE DARK SIDE OF THE MOON"

Abstract

It has been a concern since the 1950s that elderly patients undergoing surgery and anesthesia may suffer from postoperative cognitive changes. Because postoperative cognitive deterioration in the elderly may lead to serious medical and social consequences and is associated with increased morbidity, mortality, and high health care costs, the issue should be precisely addressed, and preventive strategies should be developed. An emerging body of evidence suggests that anesthesia and surgery have an undesirable effect on long-term cognitive function in the elderly; however, there are no convincing human data to support this correlation. Thus, the effects of anesthesia and surgery on cognition and on the natural course of underlying neurodegenerative diseases are not clear. This review presents a systemic and comprehensive clinical view of cognitive decline following anesthesia and surgery. It aims to emphasize the pathophysiological processes and risk factors of aging and potential anesthesia- and surgery-related neurodegeneration, since defining high-risk patients and preventing the problem can provide benefits for patients with neurodegenerative disease.

Keywords: Cognitive Dysfunction; Aging; Anesthesia; General Surgery; Alzheimer Disease; Dementia

CORRESPONDANCE
Gözde İNAN
Gazi University School of Medicine,
Department of Anesthesiology and Reanimation
Ankara, Turkey

Phone: 3122025325
e-mail: inangozde@yahoo.com

Received: 27/12/2017
Accepted: 06/03/2018

[1] Gazi University School of Medicine,
Department of Anesthesiology
and Reanimation
Ankara, Turkey

DERLEME MAKALESİ

YAŞLI BEYİNDE ANESTEZİ VE CERRAHİNİN SONUÇLARI ÜZERİNE BİR KLİNİK İNCELEME: "AYIN KARANLIK YÜZÜ"

Öz

1950'lerden beri cerrahi ve anestezi uygulanan yaşlı hastalarda postoperatif bilişsel değişiklikler yaşanması endişe kaynağı olmuştur. Yaşlılarda postoperatif bilişsel bozulma, ciddi tıbbi ve sosyal sonuçlara neden olabilir ve morbidite, mortalite ve yüksek sağlık masrafları ile ilişkili olduğundan, konu tam olarak ele alınmalı ve önleyici stratejiler geliştirilmelidir. Ortaya konan kanıtlar, anestezinin ve ameliyatın yaşlılarda uzun süreli bilişsel işlev üzerinde istenmeyen bir etkiye sahip olduğunu göstermektedir. Bununla birlikte, bu korelasyonu desteklemek için inandırıcı insan verileri mevcut değildir. Bu nedenle, anestezi ve cerrahinin kognisyon ve nörodejeneratif hastalıkların doğal seyri üzerindeki etkileri açık değildir. Bu derlemede, anestezi ve ameliyat sonrasında bilişsel bozulmanın sistemik ve kapsamlı bir klinik görünümü sunulmaktadır. Derleme, yaşlılık, potansiyel anestezi ve cerrahi ile ilişkili nörodejenerasyonun patofizyolojik süreçlerini ve risk faktörlerini vurgulamayı amaçlıyor, çünkü yüksek riskli hastaları tanımlamak ve sorunun engellenmesi nörodejeneratif hastalığı olan hastalar için fayda sağlayabilir.

Anahtar sözcükler: Bilişsel Bozulma; Yaşlılık; Anestezi; Genel Cerrahi; Alzheimer Hastalığı; Demans

INTRODUCTION

The global population is aging. As life expectancy rises, the proportion of the population aged60 or above rapidly rises. The number of people aged 60 or above worldwide is projected to double by 2050 and triple by 2100.The increase in the aging population will result in an increase in the surgery workforce, and greater longevity will pose challenges for clinicians who are likely to encounter more geriatric patients undergoing surgery (1). Despite improvements in medicine, elderly patients are proportionately more prone to peri operative complications because of physiologic changes due to aging, accompanying comorbidities, and the increased incidence of pre-existing illness and polypharmacy. As we are living longer, the incidence of age-related diseases, including neurodegenerative diseases, in particular Alzheimer's disease, is also increasing (2).

Among the many postoperative complications, postoperative cognitive dysfunction (POCD) is a vital concern that may result in increased morbidity, mortality, and health care costs (3). Cognitive dysfunction is common following anesthesia and surgery, especially in elderly patients. In most cases, cognitive function returns to baseline within a few months, but in some cases, recovery may be delayed or incomplete. Advanced age is the strongest known risk factor for the development of POCD (4). It is evident that older patients are vulnerable to developing POCD, and several factors, including premorbid cognitive status, may put them at risk. For the elderly, this complication often means a life that they can no longer manage by themselves (3).

Overview of general considerations

Postoperative cognitive changes were described in the previous century. In 1955, Bedford reported "the cerebral side effects of anesthesia on old people" as the development of confusion after surgery (5). He examined 1193 patients over the age of 50 years who underwent general anesthesia and suggested that POCD developed with an incidence of approximately 7% and that the resulting cognitive changes might be due to anesthetic agents and hypotension. Based on this idea, the results of the first international POCD research group (ISPOCD 1) were published in 1998 (6). Similar to Bedford's findings, an incidence of POCD of 10% was found. Older age, duration of anesthesia, low educational level, recurrent surgeries, postoperative infection, and respiratory complications were reported as risk factors for early POCD. Among these risk factors, age was the only statistically significant risk factor at long-term (3 months) follow-up. The same study group then searched long-term outcomes and found POCD in 1% of patients after 1 to 2 years of surveillance (ISPOCD 2). In these extensive studies, only advanced age and the type and duration of surgery were identified as possible risk factors.

Historically, all cognitive changes observed following surgery have been classified as POCD. However, to understand the underlying mechanisms and to develop prevention strategies, it is necessary to be aware of the diversity in the cognitive change spectrum and to consider interpersonal differences.

The two most common types of impairment in cognitive function are postoperative delirium (POD) and POCD. Postoperative delirium manifests with acute onset, occurs from days (often within 24 to 72 hours) to weeks following surgery, is characterized by fluctuating levels of cognition and awareness with a reduced level of focus and orientation, and is accompanied by emotional disorder and decreased psychomotor behavior (1). Postoperative delirium remains a serious and costly issue threatening public health, as it is associated with increased morbidity and mortality, prolonged cognitive impairment, and prolonged hospital stay (3). The most common tests to assess POD are the Confusion Assessment Method and the Delirium Rating Scale, which are subjective. The incidence of POD varies between 10% and 40%, rising to 50% to 65% following orthopedic, cardiac, and emergency surgeries (7,8).

Postoperative cognitive dysfunction occurs weeks or even months after surgery, and it may be prolonged (9). Unlike POD, POCD is characterized not by disorientation but by a decrease in information perception and knowledge man-

agement functions. Postoperative cognitive dysfunction does not have a uniform definition. The diagnosis requires the patient to undergo neuropsychometric testing to objectively determine the reduction in cognition when compared with preoperative baseline tests (10). The Mini-Mental State Examination (MMSE) was developed as a delirium screening test and has also been used for POCD because it takes a short time to administer; however, the questions can be learned during repeated tests. The incidence of POCD was reported to range from 8.9% to 46.1%, rising to 80% following cardiac surgery (8,11).

Dementia is classified as a chronic, irreversible, progressive neurocognitive disorder that affects both cognitive function and the performance of everyday activities. Alzheimer's disease is a neurodegenerative disease that is the most common form of dementia among the elderly. By affecting memory, problem-solving ability, decision-making, judgment, orientation, and other cognitive skills, it alters a person's ability to perform everyday activities (2). More than 5 million people in the United States older than 65 years are estimated to have Alzheimer's disease (2). Alzheimer's disease has three clinical stages: preclinical, mild cognitive impairment, and dementia. People with preclinical Alzheimer's disease are asymptomatic for up to 20 years. Although measurable biomarkers of the pathogenesis of Alzheimer's disease accompany preclinical Alzheimer's disease, there is still no formal way to diagnose the condition. Mild cognitive impairment due to Alzheimer's disease is defined as mild but measurable changes in one or more cognitive domains in comparison with the patient's previous level, greater than would be expected for the patient's age and education, without any interference with usual activities (9). In about 50% of patients, mild cognitive impairment progresses to dementia in about 5 years after diagnosis. The MMSE is a well-established cognitive screening instrument, but additional assessment of executive functions and visuospatial ability is needed for the identification of mild cognitive impairment and dementia (1).

There are certain similarities between POCD, POD, and dementia, including risk factors, clinical presentation, and pathognomonic features. Recent studies have focused on whether POD and POCD are prodromal forms of Alzheimer's disease or whether there is an association among POD, POCD, and the development of dementia; the evidence remains inconclusive (4). A recent study confirmed previous findings that elderly patients with baseline cognitive impairment at the time of surgery are at higher risk for clinically evident POD, and furthermore, elderly patients who are cognitively normal before surgery and who develop POD are more likely to develop mild cognitive impairment or dementia on follow-up than are those who do not develop POD (12). Moreover, with normal aging processes of the brain, POD, POCD, and even dementia can overlap. The course of cognitive impairment following anesthesia and surgery is schematized in Figure 1A.

The risk factors for cognitive changes of POD, POCD, and dementia are multifactorial and can be categorized as patient-related and surgery-related or nonmodifiable and potentially modifiable (Table 1). Some of these are pre-existing factors that are linked to previous fragility, while others are factors that accelerate the situation, such as stress response to trauma. Modifiable lifestyle-related risk factors are important, since controlling these factors would alter the incidence of POCD, might even reduce the incidence of Alzheimer's disease, and would ameliorate or delay the onset of and mild cognitive impairment (13). Although minor cognitive changes have been shown in younger patients, age is the main risk factor for POCD. The ability to compensate for cognitive deficits decreases with advancing age (14). Low educational level, preoperative use of narcotics and benzodiazepines, existing cognitive impairment, depressive symptoms, attention deficit, previous POD, alcoholism, visual disturbances, and electrolyte and fluid abnormalities are among the several other risk factors (7,10,14). Preoperative poor cognition, physical limitations, and accompanying systemic diseases are associated with worse postoperative outcomes. Environmental and genetic (ApoE4) risk factors are among the determinants of Alzheimer's disease (15).

Table 1. Predisposing factors, risk factors, perioperative triggers for postoperative cognitive dysfunction in the elderly.

Predisposing Factors	Cerebral	Structural Decreased brain volume Hippocampal changes Reduced neurogenesis Damaged blood-brain barrier Amyloid and/or tau accumulation
	Systemic	Inflammation Changes in levels of neurotransmitters Cerebrovascular disease Pre-operative cognitive impairment Vulnerability and reduction in cognitive reserve Advanced age Vulnerability Co-morbidities Increased incidence of pre-existing illness and polypharmacy Systemic vascular disease
	Social	Low educational level
Risk Factors	Patient-related	Advanced age Pre-operative cognitive impairment Pre-operative physical impairment, immobility Pre-operative depression, depressive symptoms, attention deficits, sleep disorders Pre-existing dementia, mild-cognitive dysfunction Pre-operative use of narcotics or benzodiazepines Cognitive impairment during hospitalization History of alcohol abuse, tobacco use Previous POCD History of stroke Vision and hearing impairment
	Surgery-related	Cardiac and/or vascular surgery Major and invasive surgery Greater surgical blood loss Greater intraoperative transfusion Longer operation duration Post-operative complications
	Non-modifiable	Advanced age Female gender Genetic risk factors (Apolipoprotein E)
	Modifiable	Vascular (DM, HT, hypercholesterolemia) Nutritional (low levels of vitamin B12 and folate, hyperhomocysteinemia) Head injuries
Perioperative Triggers	Acute pain Use of physical restraints Malnutrition, dehydration >3 medications in 24-48 h Urinary bladder catheter Anemia, intraoperative transfusion Electrolyte and fluid abnormalities	

Major and invasive surgeries (abdominal, thoracic, vascular), long duration of operation and anesthesia, and excessive blood loss increase the risk of POCD. The severity, duration, and type of the surgical procedure, particularly cardiac and orthopedic surgeries, have been associated with cognitive impairment (14). It has been discussed whether cardiopulmonary bypass, microemboli-sms, and cerebral hypoperfusion are responsible for POCD following cardiac surgery (1,4). However, similar cognitive changes were observed after off-pump cardiac surgery (1). Coronary bypass surgery has been found to cause neuronal damage due to inflammatory responses during the normothermic rewarming phase. In the cardiopulmonary bypass mouse model, limited warm-up and prolonged postoperative hypothermia have been shown to reduce the incidence of POCD (16). Hovens et al. suggested that POCD following cardiac surgery affects more extensive brain regions than does POCD following noncardiac surgery (17). Hence, POCD following cardiac surgery may be associated with a greater affected area of the brain rather than greater severity (17).

Pathophysiology and potential mechanisms

Various hypotheses have been proposed for the pathophysiology of POCD Neurotransmitters, inflammation, psychological stress, metabolic changes, electrolyte imbalance, and genetic factors are thought to cause damage to neuronal functioning (3). However, the pathophysiology of POCD is not yet fully understood. Most of the risk factors are up-regulated by aging.

Acetylcholine, melatonin and norepinephrine are some mediators that have been shown to correlate with delirium. Neuroinflammation has been hypothesized to underlie the mechanism of the development of POCD (18,19). Inflammation in the periphery due to surgical trauma is transferred to the central nervous system and causes glial activation, exaggerated expression of proinflammatory mediators within the central nervous system, and neural dysfunction (19). Aging itself creates glial alterations, and the cause of the transition from normal aging glia to pathologic glia remains unclear. It is suspected that events during an individual's early life, including infection, stress, and nutrition, can impact immune reactivity within the brain and cause subsequent exaggerated glial activation called "glial priming" for the remainder of life, thereby altering cognition and increasing the risk of neuroinflammatory disorders, POCD, and Alzheimer's disease (20). In rats made vulnerable by infection early in life, even aging has been shown to impact glial reactivity (18,19). Proinflammatory cytokines involved in neuroinflammation are thought to cause neuronal damage. In a study that compared the occurrence of POD in elderly patients undergoing minimally invasive laparoscopic surgery versus open colon surgery, significantly higher levels of inflammatory markers were found in patients receiving open surgery, a result consistent with a higher stress response in this group of patients (21).

Association between anesthesia and surgery

Several studies have tried to clarify the role of anesthetics in the pathophysiology of POCD. There are still no conclusive human data to support this correlation. This hypothesis has been supported only by experimental and in vitro models. The mechanism of cognitive impairment after surgery is not clear. Since distinguishing the effects of surgery and anesthesia on POCD is not possible, these two factors are considered together. Animal studies emphasize that surgery creates an inflammatory response, which plays a significant role (18). Peripheral surgery activates inflammatory cytokines and impairs the integrity of the blood–brain barrier, allowing macrophages to easily migrate into the hippocampus and cause memory problems.

The effects of anesthesia on POCD have been attributed to potential neurotoxicity of anesthetics that exacerbates age-related neuronal changes such as losses in cerebral reserve and increased permeability of the blood–brain barrier. The pivotal mechanism causing cognitive decline is abnormal deposition of naturally occurring peptides in the

brain. Anesthesia-related POCD shares this common pathological mechanism through amyloid beta (Aβ) deposition and tau phosphorylation (22,23). Preclinical data suggest that inhalation anesthetics, in particular isoflurane and sevoflurane, increase the production, precursors, and accumulation of Aβ, which results in caspase activation, mitochondrial damage, and ultimately apoptosis (24,25). In contrast, desflurane and nitrous oxide have not been shown to enhance Aβ accumulation invivo or invitro (26,27). Additional studies are necessary to determine the superiority of desflurane over isoflurane or sevoflurane in regard to neurotoxicity (28).

Tau phosphorylation causes formation of neurofibrillary tangles, the other pathologic hallmark of Alzheimer's disease. Anesthesia-induced hypothermia may be a mediator of tau hyperphosphorylation (29). However, both volatile anesthetics and propofol also induce tau production and phosphorylation under normothermic conditions (23).

Given the significant role of inflammation in the pathogenesis of POCD, anesthetic drugs could affect cognitive decline via their effects on inflammation and the immune system. Studies have found divergent findings for the anti-inflammatory effects of volatiles versus propofol (30). Calcium metabolism also plays some role in the pathogenesis of Alzheimer's disease. High levels of volatile anesthetics are reported to increase intracellular calcium levels and cause excitotoxic neuronal injury in cultured neuronal cells.

Clinical epidemiological studies investigating whether anesthesia and surgery increase the risk of developing Alzheimer's disease are limited. Retrospective cohort and case-control studies have been used to investigate a possible link, and the results are conflicting (Table 2). Seitz et al. in a review investigated the epidemiological evidence for GA as a risk factor for Alzheimer's disease and concluded that there was not sufficient evidence to show a relationship (42). On the basis of population-based case-control studies, some authors suggest that exposure to anesthetics increases the risk of Alzheimer's disease, whereas other authors suggest that it does not (36,40).

Identifying high-risk patients, prevention, and anesthesia management

A review focusing on preventive factors for Alzheimer's disease suggested that any interventions that can delay the onset of the disease will play a major role in delaying the onset of clinical Alzheimer's disease (43). Patients at risk should be identified preoperatively. Frailty assessment and identification of high-risk patients may include the use of biomarkers, cognitive tests, imaging, and genome studies (15,44). Surgery and anesthesia may be associated with some biomarkers of neuronal injury, such as increases in total and phosphorylated tau and decrease in Aβ in cerebrospinal fluid. Imaging with computed tomography, magnetic resonance, and single-photon emission computed tomography is also recommended for screening vulnerable surgical patients (9). Nevertheless, the correlations between changes in biomarkers and cognitive deficits are unclear, and further studies are warranted to interpret their relevance to clinical outcomes. High-risk patients who may benefit from geriatrics consultation are listed in Table 3.

The multifactorial etiology of POCD necessitates multimodal interventions to reduce its incidence. Preventive measures for POCD may be classified as preoperative, perioperative, and postoperative (Figure 1B). In particular, preoperative preventive programs aim at controlling risk factors, mainly focusing on hearing and vision problems, cognitive problems, sleep disturbances, immobility and dehydration, and nutrition, and they recommend fluid support, exercise programs, mind exercises, orientation studies, and nonpharmacological sleep regulators (45). Perioperative measures include maintaining homeostasis, avoiding long-acting benzodiazepines, preferring minimally invasive surgeries with short operative duration, optimizing anesthetics, early recovery, and optimal pain relief (14).

Table 2. Clinical studies on the association between exposure to anesthesia and surgery and risk of dementia.

Study	Design	Number or Type of Study Subjects	Type of Surgery/ Anesthesia	Findings
Pálotas et al(31)	Biomarker studies	30	CABG	CSF Aβ decreased Injury biomarkers (S100B, tau) elevated at 6 months
Tang et al(32)	Biomarker studies 11		Idiopathic nasal CSF leak repair	Total-tau/$A\beta_{1-42}$ ratio in CSF increased Proinflammatory cytokines, IL-6, TNF-α, and IL-10 elevated postoperatively
Shiiya et al(33)	Biomarker studies	28	Prosthetic replacement of the descending thoracic or thoracoabdominal aorta	CSF tau and S100beta only increased in individuals with brain infarction or transient neurologic dysfunction
Reinsfelt et al(34)	Biomarker studies	10	Cardiac valve replacement surgery with cardiopulmonary bypass	Levels of S100beta and glial fibrillary acidic protein increased by 35% postoperatively Total tau, neurofilament light chain protein, and neuron-specific enolase did not change significantly IL-6 and IL-8 in the CSF increased significantly after anesthesia and surgery
Seitz et al(35)	Retrospective case-control studies (A meta-analysis of 15 case-control studies)	1.752 cases and 5.261 controls	GA	No statistically significant association between GA and the development of AD
Sprung et al(36)	Retrospective case-control studies	877 Patients with incident dementia recorded between 1985-1994	GA	A total of 70% of the dementia patients had been exposed to GA compared with 72.5% of the control group No significant association between exposure to GA >45 years and the diagnosis of dementia
Chen et al(37)	Retrospective case-control studies	5.345 patients >50 years 21.380 controls Patients who were newly diagnosed with dementiaand individuals without dementia for control group from 2005-2009	GA exposure was categorized into three subtypes: endotracheal tube intubation GA (ETGA), intravenous injection GA (IVGA), or intramuscular injection	GA (IMGA), versus heavy sedation Individuals exposed to surgery under ETGA were found to be at significantly higher risk of developing dementia in a dose-dependent response

Lee et al(38)	Cohort studies	119 patients (CABG=78; PTCA=41) >55 years without a diagnosis of dementia prior to surgery	One group underwent CABG under GA The other group received sedation for PTCA	5-year follow-up, patients who had undergone CABG and GA had a 1.7-fold increased risk of developing AD compared with those who only received sedation and PTCA
Vanderweyde et al(39)	Cohort studies	Subjects undergoing hernia operations (under GA (N= 2,658) or local (N = 1,111) anesthesia, as well as subjects undergoing prostate operations under GA (N = 2,820) or local (N = 3,691) anesthesia	Prostate or hernia surgery under either GA or RA	Patients who had received GA developed dementia less frequently than those who had received RA
Chen et al(40)	Cohort studies	24.901 patients >50 years who were anesthetized for the first time from 2004-2007 Control group 110.972 patients	GA or RA	Follow-up period of 3-7 years, risk of dementia in the anesthesia group was found significantly higher than that in the control group Both exposure to GA and to regional anesthesia yielded increased risks of incident dementia Patients who undergo anesthesia and surgery may be at increased risk for developing dementia
Liu et al(41)	Prospective studies	180 aMCI patients 60 aMCI outpatients as the control group	Lumbar spinal surgery Sevoflurane, propofol, or lidocaine epidural anesthesia	2-year follow-up, the number of aMCI patients who progressed to AD did not differ between the groups The number of patients who exhibited progression of aMCI was greater in the sevoflurane group than in the control group
AielloBowles et al (11)	Prospective studies	3.988 Community-dwelling members of the adult changes in thought cohort >65 age, free of dementia at baseline	Participants self-reported all prior surgical procedures with GA or neuraxial anesthesia at baseline and reported new proceduresevery 2 years	High-risk surgery with general anesthesiawas not associated with greater risk of dementia than no history of anesthesia Anesthesia exposure was not associatedwith of dementia or AD in older adults

CSF; Cerebrospinal fluid
CABG; Coronary artery bypass grafting
GA; General anesthesia
PTCA; Percutaneous transluminal coronary angioplasty
RA; Regional anesthesia
aMCI; Amnestic mild cognitive impairment

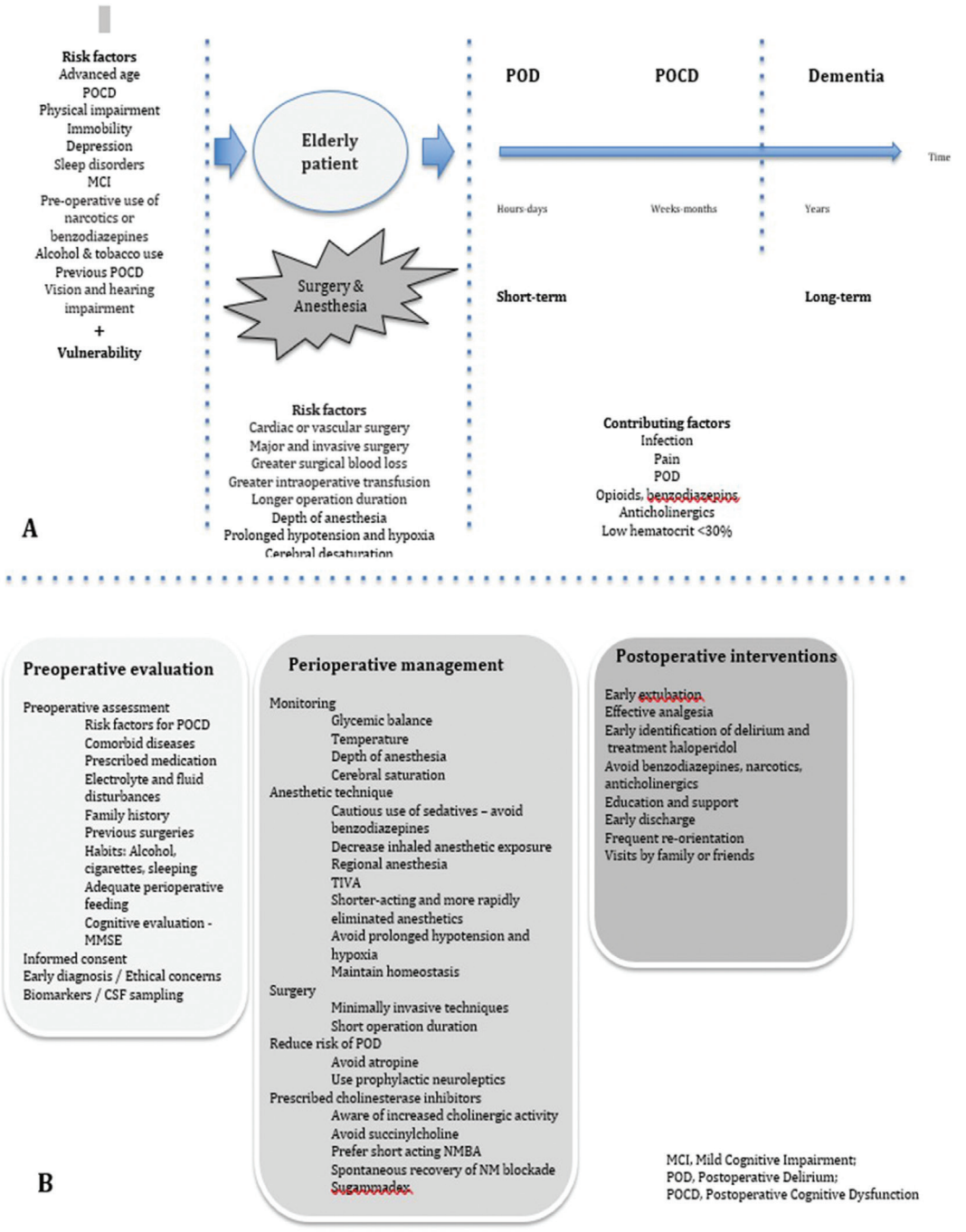

Figure 1A. Schema of postoperative cognitive dysfunction with preoperative and peroperative risk factors and postoperative contributing factors. **1B.** Preoperative evaluation, perioperative management and postoperative interventions as preventive measures for postoperative cognitive dysfunction.

Table 3. Patient features for pre-operative geriatrics consultation.

Age > 80 years
Baseline cognitive dysfunction or dementia
Multiple medical comorbidities
Chronic use of psychotropic medications
Dependence on alcohol or other drugs
Poor social support
Hearing or vision impairment
Immobility or history of functional decline
Recurrent hospitalizations within the last year
Urgent or emergent surgery
Prolonged hospital and/or ICU stay

Controlling chronic hypoperfusion of the brain and triggered neuroinflammation by treating comorbid disease conditions (hypertension, diabetes, hypoxia, obstructive sleep apnea, obesity, vitamin B_{12}–folate deficiency, depression, traumatic brain injury) may enhance cognition (46). Because chronic systemic inflammation promotes aging of glia through excessive neuroinflammation, it is argued that antioxidant nutrients may be beneficial for preventing aging of glia, thereby improving cognitive functions (20). Hypothetically, environmental stimuli (toxins, drugs of abuse, dietary fatty acids) might also trigger neurodegeneration via inflammation in long-term outcomes (19). However, based on the accumulating data on inflammation and POCD, studies seeking anti-inflammatory agents for prevention of POCD have not been successful to date.

Some studies have proposed that avoiding general anesthesia by preferring regional anesthesia techniques would promote cognitive functions in the elderly (47). Nevertheless, most studies have suggested that the occurrence of POCD is irrespective of the type of anesthetic technique (47-51). Lack of evidence for any difference between regional and general anesthetic techniques can be explained by the use of intravenous sedation during regional anesthesia (52). Among general anesthetics, volatile anesthetics have been suggested to be associated with a higher rate of POCD than propofol by animal studies. Optimizing anesthesia by monitoring the depth of anesthesia and cerebral oxygenation has been advocated to reduce the risk of POCD (7). For those patients who are more sensitive to anesthetics, deep anesthesia has been associated with a higher rate of POD (9).

It has been suggested in the literature that because both patients with mild cognitive impairment and those with dementia have increased sensitivity to anesthetics, surgery and anesthesia can worsen their symptoms (6). The main question will be how to provide the best perioperative care for patients who are at high-risk or who already have mild cognitive impairment or dementia. A consensus statement from the First International Workshop on Anesthetics and Alzheimer's Disease initially shed some light on this possible link and provided some recommendations (53). A tailored anesthesia is needed for surgical patients of advanced age with

underlying neurodegenerative disease: choosing total intravenous anesthesia, avoiding inhalational agents and benzodiazepines, monitoring the depth of anesthesia and if possible brain oxygenation, monitoring and controlling temperature and glycemia, and considering early extubation with a multimodal postoperative analgesic plan (23,54,55). In the only randomized study, Liu et al. (41) evaluated whether exposure to anesthetics induces progression of mild cognitive impairment. The authors concluded that sevoflurane anesthesia accelerated cognitive decline, and they recommended regional anesthesia or intravenous anesthesia with propofol rather than volatile anesthetics for patients with pre-existing Alzheimer's disease. This finding is consistent with the preclinical data that suggest a greater production of Aβ by volatile anesthetics, as discussed above.

In conclusion, the extent of cognitive decline following surgery and anesthesia has a significant impact on patient health and is substantially associated with prolonged recovery, greater morbidity, and loss of independence in these patients. Recognition of the risk factors will provide us with better prevention and management strategies to provide the best care for elderly patients who have or are at high-risk for POCD. In summary, possible strategies for the prevention and treatment of postoperative cognitive impairment in elderly patients include the use of perioperative cognitive education, geriatric consultation for high-risk patients, cooperation with family members to promote early rehabilitation, preference for minimally invasive surgical techniques, careful use of sedative premedication drugs, preference for short-acting anesthetic agents, maintenance of fluid, electrolyte, and glycemic homeostasis, and use of electroencephalogram. In the elderly patient, especially in the presence of other comorbid diseases, the surgical decision should be made carefully while considering possible cognitive deterioration. A multidisciplinary perioperative approach, with collaboration between surgery, anesthesiology, and geriatrics, is a necessity in caring for geriatric patients.

Acknowledgement

The authors have no conflict of interest to disclose.

REFERENCES

1. O' Brien H, Mohan H, Hare CO, Reynolds JV, Kenny RA. Mind over matter? The hidden epidemic of cognitive dysfunction in the older surgical patient. Ann Surg 2017;265(4):677-91. (PMID:27537541).
2. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimer's Dement 2016;12(4):459-509. (PMID:27570871).
3. Müller A, Lachmann G, Wolf A, Mörgeli R, Weiss B, Spies C. Peri-and postoperative cognitive and consecutive functional problems of elderly patients. Curr Opin Crit Care 2016;22:406-11. (PMID:27272100).
4. Steinmetz J, Rasmussen LS. Peri-operative cognitive dysfunction and protection. Anaesthesia 2016;71:58-63. (PMID:26620148).
5. Bedford PD. Adverse cerebral effects of anaesthesia on old people. Lancet 1955;269(6884):259-63. (PMID:13243706).
6. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998;351(9106):857-61. (PMID:9525362).
7. Strøm C, Rasmussen LS, Sieber FE. Should general anaesthesia be avoided in the elderly? Anaesthesia 2014;69:35-44. (PMID:24303859).
8. Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. Front Aging Neurosci 2015;7:112. (PMID:26106326).
9. Berger M, Burke J, Eckenhoff R, Mathew J. Alzheimer's disease, anesthesia, and surgery: a clinically focused review. J Cardiothorac Vasc Anesth 2014;28(6):1609-23. (PMID:25267693).
10. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth 2009;103:i41-6. (PMID:20007989).
11. Aiello Bowles EJ, Larson EB, Pong RP, et al. Anesthesia exposure and risk of dementia and Alzheimer's disease: a prospective study. J Am Geriatr Soc 2016;64(3):602-7. (PMID:26865152).

12. Sprung J, Roberts RO, Weingarten TN, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth 2017;119(2):316-23. (PMID:28854531).

13. Daulatzai MA. "Boomerang neuropathology" of late-onset Alzheimer's disease is shrouded in harmful "BDDS": breathing, diet, drinking, and sleep during aging. Neurotox Res 2015;28(1):55-93. (PMID:25911292).

14. Hartholt KA, van der Cammen TJ, Klimek M. Postoperative cognitive dysfunction in geriatric patients. Z Gerontol Geriatr 2012;45(5):411-6. (PMID:22538789).

15. Terrando N, Brzezinski M, Degos V, et al. Perioperative cognitive decline in the aging population. Mayo Clin Proc 2011;86(9):885-93. (PMID:21878601).

16. de Lange F, Jones WL, Mackensen GB, Grocott HP. The effect of limited rewarming and postoperative hypothermia on cognitive function in a rat cardiopulmonary bypass model. Anesth Analg 2008;106(3):739-45. (PMID:18292411).

17. Hovens IB, van Leeuwen BL, Mariani MA, Kraneveld AD, Schoemaker RG. Postoperative cognitive dysfunction and neuroinflammation; cardiac surgery and abdominal surgery are not the same. Brain Behav Immun 2016;54:178-93. (PMID:26867718).

18. Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. Brain Behav Immun 2014;38:202-10. (PMID:24517920).

19. Bilbo SD, Smith SH, Schwarz JM. A lifespan approach to neuroinflammatory and cognitive disorders: a critical role for glia. J Neuroimmune Pharmacol 2012;7(1):24-41. (PMID:21822589).

20. Wu Z, Yu J, Zhu A, Nakanishi H. Nutrients, Microglia Aging, and Brain Aging. Oxid Med Cell Longev 2016;2016:7498528. (PMID:26941889).

21. Tan CB, Ng J, Jeganathan R, et al. Cognitive changes after surgery in the elderly: does minimally invasive surgery influence the incidence of postoperative cognitive changes compared to open colon surgery? Dement Geriatr Cogn Disord 2015;39(3-4):125-31. (PMID:25471533).

22. Fodale V, Santamaria LB, Schifilliti D, Mandal PK. Anaesthetics and postoperative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. Anaesthesia 2010;65(4):388-95. (PMID:20136805).

23. Inan G, Özköse Satirlar Z. Alzheimer disease and anesthesia. Turk J Med Sci 2015;45(5):1026-33. (PMID:26738343).

24. Xie Z, Xu Z. General anesthetics and β-amyloid protein. Prog Neuropsychopharmacol Biol Psychiatry 2013;47:140-6. (PMID:22918033).

25. Zhou R, Bickler P. Interaction of isoflurane, tumor necrosis factor-α and β-amyloid on long-term potentiation in rat hippocampal slices. Anesth Analg 2017;124(2):582-7. (PMID:28099324).

26. Zhang Y, Xu Z, Wang H, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol 2012;71(5):687-98. (PMID:22368036).

27. Zhen Y, Dong Y, Wu X, et al. Nitrous oxide plus isoflurane induces apoptosis and increases beta-amyloid protein levels. Anesthesiology 2009;111(4):741-52. (PMID:19741497).

28. Jiang J, Jiang H. Effect of the inhaled anesthetics isoflurane, sevoflurane and desflurane on the neuropathogenesis of Alzheimer's disease (review). Mol Med Rep 2015;12(1):3-12. (PMID:25738734).

29. Whittington RA, Papon MA, Chouinard F, Planel E. Hypothermia and Alzheimer's disease neuropathogenic pathways. Curr Alzheimer Res 2010;7(8):717-25. (PMID:20678067).

30. Wu X, Lu Y, Dong Y, et al. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-α, IL-6, and IL-1β. Neurobiol Aging 2012;33(7):1364-78. (PMID:21190757).

31. Palotás A, Reis HJ, Bogáts G, et al. Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid. J Alzheimers Dis 2010;21(4):1153-64. (PMID:21504113).

32. Tang JX, Baranov D, Hammond M, et al. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology 2011;115(4):727-32. (PMID:21857497).

33. Shiiya N, Kunihara T, Miyatake T, Matsuzaki K, Yasuda K. Tau protein in the cerebrospinal fluid is a marker of brain injury after aortic surgery. Ann Thorac Surg 2004;77(6):2034-8. (PMID:15172260).

34. Reinsfelt B, Ricksten SE, Zetterberg H, Blennow K, Fredén-Lindqvist J, Westerlind A. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. Ann Thorac Surg 2012;94(2):549-55. (PMID:22698770).

35. Seitz DP, Shah PS, Herrmann N, Beyene J, Siddiqui N. Exposure to general anesthesia and risk of Alzheimer's disease: a systematic review and meta-analysis. BMC Geriatr 2011;11:83. (PMID:22168260).

36. Sprung J, Jankowski CJ, Roberts RO, et al. Anesthesia and incident dementia: a population-based, nested, case-control study. Mayo Clin Proc 2013;88(6):552-61. (PMID:23642337).

37. Chen CW, Lin CC, Chen KB, Kuo YC, Li CY, Chung CJ. Increased risk of dementia in people with previous exposure to general anesthesia: a nationwide population-based case-control study. Alzheimers Dement 2014;10(2):196-204. (PMID:23896612).

38. Lee TA, Wolozin B, Weiss KB, Bednar MM. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal angioplasty. J Alzheimers Dis 2005;7(4):319-24. (PMID:16131734).

39. Vanderweyde T, Bednar MM, Forman SA, Wolozin B. Iatrogenic risk factors for Alzheimer's disease: surgery and anesthesia. J Alzheimers Dis 2010;22(3):91-104. (PMID:20858967).

40. Chen PL, Yang CW, Tseng YK, et al. Risk of dementia after anaesthesia and surgery. Br J Psychiatry 2014;204(3):188-93. (PMID:23887997).

41. Liu Y, Pan N, Ma Y, et al. Inhaled sevoflurane may promote progression of amnestic mild cognitive impairment: a prospective, randomized parallel-group study. Am J Med Sci 2013;345(5):355-60. (PMID:23044653).

42. Seitz DP, Reimer CL, Siddiqui N. A review of epidemiological evidence for general anesthesia as a risk factor for Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2013; 47:122-7. (PMID:22771690).

43. Selekler K. Are there preventive factors in Alzheimer's disease? Part: I. Antioxidants, non-steroïd anti-inflamatory drugs, estrogen and statins. Turkish Journal of Geriatrics 2007;10(2):88-99. (In Turkish).

44. Karadas O, Koc G, Ozon AO, Ozturk B, Konukoglu D. Biomarkers of Alzheimer's disease and vascular dementia simultaneously sampled from serum and cerebrospinal fluid. Turkish Journal of Geriatrics 2017;20(1):1-7.

45. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium. Eur J Anaesthesiol 2017;34(4):1-23. (PMID:28187050).

46. Daulatzai MA. Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. J Neurosci Res 2017;95(4):943-972. (PMID:27350397).

47. Mason SE, Noel- Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post- operative cognitive dysfunction and post- operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 2010;22(3):67-79. (PMID:20858956).

48. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47(3):260-6. (PMID:12648190).

49. Atay IM, Aslan A, Atay T, Burc H. Prevalence of delirium, risk factors and cognitive functions in elderly hip fracture patients with general and spinal anesthesia. Turkish Journal Of Geriatrics 2012;15(3):273-8. (in Turkish).

50. Wu CL, Hsu W, Richman JM, Raja SN. Postoperative cognitive function as an outcome of regional and general anaesthesia. Reg Anesth Pain Med 2004;29(3):257-68. (PMID:15138912).

51. Ilango S, Pulle RC, Bell J, Kuys SS. General versus spinal anaesthesia and postoperative delirium in an orthogeriatric population. Australas J Ageing 2016;35(1):42-7. (PMID:26364948).

52. Vanderweyde T, Bednar MM, Forman SA, Wolozin B. Iatrogenic risk factors for Alzheimer's disease: surgery and anesthesia. J Alzheimers Dis 2010;22(3):91-104. (PMID:20858967).

53. Baranov D, Bickler PE, Crosby GJ, et al. First international workshop on anesthetics and Alzheimer's disease consensus statement: first international workshop on anesthetics and Alzheimer's disease. Anesth Analg 2009;108(5):1627-30. (PMID:19372347).

54. Lobo FA, P Saraiva A. Playing games with the brain: the possible link between anesthesia and Alzheimer's disease revisited. Rev Esp Anestesiol Reanim 2014;61(8):417-21. (PMID:25171825).

55. Chan MT, Cheng BC, Lee TM, Gin T, CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25(1):33-42. (PMID:23027226).