Research Article

Postoperative Cognitive Dysfunction in Elderly: A Literature Review

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Abstract

The increasing number of older adults undergoing surgery poses significant challenges for clinicians involved in perioperative care, particularly regarding the risk of postoperative cognitive impairment. Postoperative cognitive dysfunction (POCD) in the elderly is notably more prevalent and associated with poor outcomes, highlighting the need for effective management strategies. As neuroinflammation has been described as a fundamental mechanism in neurodegenerative diseases, this literature review summarizes the role of neuroinflammation in relation to surgical stress and age-related changes, identifies risk factors, with emphasis on preventive care through comprehensive assesment, prehabilitation and optimisation during the perioperative period to preserve cognitive function.

Keywords: postoperative cognitive dysfunction, neuroinflammation, elderly health, geriatric, vulnerable population, cognitive therapy, good health and well-being.

Introduction

Demographic shifts, marked by an increasing proportion of older adults, have led to an increasing numbr of older patients undergoing surgical procedures.[1,2] Perioperative care of older adults requires comprehensive management because aging is linked to a decline in physiological capacity, which makes older individuals susceptible to surgical complications.[2,3] A prevalent postoperative complication among the elderly is neurocognitive dysfunction, which manifests as postoperative delirium (POD) and postoperative cognitive dysfunction (POCD).[4]

POCD is defined as cognitive decline that emerges after the immediate effects of surgery and anesthesia have subsided. It may present with subtle clinical features and lack subjective symptoms, often leading to underdiagnosis.[5] The incidence of POCD in older patients undergoing non-cardiac surgery ranges from 2.2% to 35.7%, with higher rates observed in cardiac surgery and in older age groups.[6,7] POCD is associated with poor postoperative recovery, increased dependence on social and financial support, functional decline, and increased mortality.[8]

Neuroinflammation, which has been implicated in the pathogenesis of neurodegenerative diseases, has been extensively studied for its role in POCD pathophysiology.[9] However, no diagnostic tools or standard evidence-based therapies are currently available for POCD.[5,10] Although typically transient, recent evidence suggests that POCD may progress to an irreversible neurodegenerative state in susceptible individuals, highlighting its significance.[11] This literature review aimed to describe the pathogenesis, diagnosis, and management of POCD in older adults. Understanding this issue is crucial because POCD is a preventable condition with significant implications for patients' quality of life and healthcare costs.

Definition of POCD

POCD refers to a reduction in cognitive abilities evaluated through neurophysiological reassessment conducted after surgical interventions.[12,13] The Nomenclature Consensus Working Group has suggested revised terminology for cognitive disorders that occur during the perioperative period. This revised terminology, known as perioperative neurocognitive disorder (PND), is intended to align with the diagnostic criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[14] A significant distinction between PND and POCD is that PND requires subjective complaints accompanied by evidence of functional impairment, as outlined in the DSM-5. In contrast, POCD is identified through objective evaluation of cognitive domains, independent of subjective symptoms.[13,15] Despite the introduction of this new terminology, POCD remains used in research as a means of objectively characterizing postoperative cognitive decline. [12,13,15]

Aging and brain susceptibility to neuroinflammation

The interaction between surgical stress and age-related changes contributes to neuroinflammation.[16] Age-related changes enhance the activity of the innate immune system due to ineffective debris clearance, dysbiosis, and dysregulation of complement activation.[17–19] Macrophages are polarized towards an inflammatory phenotype, characterized by increased basal secretion of Interleukin-1B (IL-1B), tumor necrosis factor alpha (TNF-α), Interleukin-6 (IL-6), C-X-C motif chemokine ligand 9 (CXCL9), and CXCL10, even in the absence of stimulation.[17,19] Mitochondrial dysfunction and accumulation of senescent cells occur with aging. In mitochondria, oxidative phosphorylation is disrupted, leading to elevated levels of reactive oxygen species (ROS) and the release of mitochondrial damage-associated molecular patterns (mtDAMP)s.[19] These mtDAMPs activate innate immune sensors, such as the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, a cytosolic multiprotein complex that plays an effector role in the inflammatory cascade, resulting in a heightened sensitized state.[18,20]

The accumulation of senescent cells can initiate age-related pathologies characterized by impaired cell function and chronic inflammation through increased autocrine and paracrine secretion of the proinflammatory senescence-associated phenotype (SASP). Senescence can occur in neurons, astrocytes, oligodendrocytes, and microglia, which are integral to central nervous system (CNS) immunity, neuron survival, and synaptic plasticity.[17,18] With aging, dysregulation of tight junctions affects the permeability of the blood-brain barrier (BBB), exposing the CNS to the risk of inflammation.[18,21]

Pathophysiology of neuroinflammation and cognitive impairment in POCD

Surgical trauma prompts the release of damage-associated molecular patterns (DAMPs), notably the high mobility group box 1 protein (HMGB1). HMGB1 binds to pattern recognition receptors (PRRs), such as Toll-like receptor (TLR)-4 and receptor for advanced glycosylation end products (RAGE), located on the cell membranes of bone marrow-derived monocytes (BMDMs) and macrophages in the peripheral circulation.[9,11,21,22] This interaction activates nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression and release of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, thereby initiating the inflammatory response. The release of HMGB1 further amplifies inflammation through a positive feedback loop influenced by IL-1β, IL-6, and TNF-α.[9] Other released DAMPs, such as S100A8, S100A12, and C-reactive protein (CRP), contribute to inflammation by binding to their respective PRRs.[23]

Systemic inflammation, initiated by the release of IL-1, IL-6, and TNF-α into the systemic circulation, expands to the CNS via neural and humoral pathways.[22] Inflammatory mediators may directly enter the CNS through passive diffusion in the periventricular area or active transport.[17,22] The BBB experiences increased permeability and damage to tight junctions due to prostaglandin and matrix metalloproteinase (MMP), which are synthesized and expressed in response to cytokines IL-1β and TNF-α.[9,11,21,22,24] Systemic inflammatory mediators bind to vagal afferents, facilitating the release of the neurotransmitter glutamate and activation of mast cells within the CNS.[22,23] A breach in the BBB permits cytokines to infiltrate the CNS, and through the interaction between chemokines, such as monocyte chemoattractant protein 1 (MCP-1) or C-C motif ligand 2 (CCL2), and the BMDM cell surface receptor chemokine receptor type 2 (CCR2), BMDMs are recruited to the CNS from systemic circulation.[9,24] Within the CNS, BMDMs secrete proinflammatory cytokines and activate microglia.[9,11,23] Furthermore, mast cells activated by the vagal nerve release mediators that induce neuroinflammation and activate microglia.[22,23]

When activated by peripheral immune signals, microglia, in conjunction with astrocytes, contributes to a cycle that culminates in neuronal damage and cognitive impairment. Activated microglia secrete mediators, such as IL-1B, IL-6, and TNF-α, leading to inflammation within the CNS. The released inflammatory cytokines subsequently activate additional microglia, perpetuating a cycle that intensifies central inflammation.[9,11,23] Microglia can activate astrocytes through the phosphoinositide 3-kinase (P13K)/protein kinase B (ALK)/mammalian target of rapamycin (mTOR) and NF-κB pathways. Conversely, endoplasmic reticulum (ER)-stressed astrocytes can activate microglia via paracrine signaling. Together, they release pro-inflammatory cytokines, further compromising the BBB and upregulating the expression of MCP-1/CCL2, which facilitates chemotaxis, enhances the recruitment of BMDM, and extends the CNS inflammatory cycle.[11,17]

The hippocampus, a critical region for learning and memory formation, contains numerous PRRs for inflammatory factors, such as TNF-α and IL-1β, rendering it susceptible to inflammation.[9,22] The presence of inflammatory mediators within the CNS inhibits brain-derived neurotrophic factor (BDNF), which is essential for neuron survival, signal transmission, and synaptic plasticity across various brain regions, and impairs tropomyosin receptor kinase B (TrkB)-mediated memory formation.[17,22,23] Neuroinflammation leads to the overactivation of N-methyl-D-aspartate receptors (NMDARs), resulting in the cleavage of the full-length B-type

tyrosine kinase receptor (TrkB-FL) and dysfunction of the BDNF/TrkB signaling pathway, which are crucial for the regulation and transmission of synaptic signals and long-term potentiation (LTP) in the hippocampus .[9,17,22]
Postoperative cognitive impairment has also been attributed to oxidative and nitrosative stress and glutamate excitotoxicity. Neuroinflammation prompts neurotoxic glial cells to release ROS and nitric oxide (NO). Oxidative stress inhibits mitochondrial respiratory enzymes and induces DNA damage, leading to apoptosis.[9,23] The release of HMGB1 following injury enhances glutamate influx into hippocampal neurons, leading to glutamate toxicity. This condition is exacerbated by glutamate secretion from active astrocytes, leading to excitotoxicity and neuronal death .[17,23] Prolonged stress results in protein misfolding. When autophagy is ineffective, such as in aging, damaged organelles, lipids, and proteins accumulate, leading to microenvironmental toxicity. Autophagic dysfunction also activates inflammasomes which triggers an inflammatory form of programmed cell death, contributes to neuronal damage.[22,24]
Although neuroinflammation-driven processes are typically transient, neurodegenerative processes can occur in susceptible individuals. In those with risk factors, such as the apolipoprotein E (ApoE) gene, especially the ε4 allele carrier status or mild cognitive impairment (MCI), POCD may progress to an amplification phase, transitioning into a chronic neurodegenerative state.[11,25] Inflammatory amplification contributes to neurodegeneration through the accumulation of amyloid beta (Aβ), proteinopathies, and synaptic failure. Impaired microglial autophagy, along with an active inflammasome, promotes increased Aβ production, leading to extracellular amyloid deposition that induces synaptic toxicity and apoptosis. Furthermore, inflammation triggers tau hyperphosphorylation through kinases resulting in the loss of structural and functional proteins, culminating in synaptic injury..[11,26]

Gut dysbiosis and POCD

Gut microbiota play a role in CNS immune modulation through the synthesis of neurotransmitters and neuromodulators, which are involved in the modulation of neurons and glial cells.[23,27] Dysbiosis may arise from stress, inflammation induced by surgical procedures, and medications used during the perioperative period. With advancing age, there is a reduction in microbiota diversity, decrease in commensal bacteria, and diminished synthesis, resulting in the loss of beneficial effects from the gut biota.[28] Inflammation and surgical stress can compromise intestinal permeability by affecting tight junctions through the action of IL-6 and catecholamines. Stress during the perioperative period, such as anxiety, insomnia, and malnutrition, can contribute to increased catecholamine and cortisol levels, which can affect gut permeability.[27] This disruption permits the translocation of microbes and their molecules into the circulation, thereby activating the immune system and intensifying the inflammatory response.[23,27,28]

Role of cholinergic anti-inflammatory pathway

The cholinergic pathway is integral to cognitive function due to its anti-inflammatory and protective effects, which regulate and mitigate neuroinflammation. Age-related changes affect cholinergic tone, receptor density, and functionality. These changes, together with microglial priming and diminished neural plasticity, may lead to delayed recovery and extended cognitive decline.[29] The alpha-7 nicotinic acetylcholine receptor (α7 nAChR) is pivotal in resolving inflammation and facilitating cognitive recovery through autophagy-mediated clearance of damaged proteins and organelles, as well as decreased ROS production.[23] The vagal nerve releases acetylcholine (ACh), which binds to the α7 nAChR, leading to reduced pro-inflammatory cytokine production via NF-κB inhibition. α7 nAChR receptors are prevalent throughout the central nervous system, particularly in the prefrontal cortex and hippocampus, and are involved in the regulation of cognition, memory, learning, and emotion.[24]
Vagal stimulation can promote the induction of regulatory T cells and secretion of the anti-inflammatory cytokine IL-4, which promotes microglial differentiation into an anti-inflammatory phenotype and secretion of the anti-inflammatory cytokine IL-10.[9,22] The cholinergic pathway also modulates the activity of anti-inflammatory lipid mediators, such as resolvins, lipoxins, and macrophage mediators, in resolving inflammation and supports the restoration of blood-brain barrier integrity through netrin-1, a protein involved in cell migration.[9] Inflammation associated with the degeneration of central cholinergic neurons has been observed in several neurological disorders, including delirium, Parkinson's disease, stroke, and brain injury. Microglia and astrocytes express AChRs. With aging and severe inflammation, the number and function of cholinergic receptors on microglia are altered, resulting in impaired anti-inflammatory signaling pathways.[29]

Risk factors of POCD

The risk factors for postoperative cognitive dysfunction (POCD) can be patient-related, surgical or intraoperative, or postoperative. Patient-related risk factors include advanced age, low educational attainment, pre-existing cognitive impairment, and comorbidities, particularly vascular comorbidities such as diabetes mellitus (DM), stroke, and hypertension (HT).[16,30–33] These factors contribute to increased vulnerability, reduced brain resilience, and diminished compensatory capacity in response to surgical stress and anesthesia. Although no sex-based differences were observed, men carrying the ApoE gene, especially the ε4 allele, had a higher incidence and severity of cognitive impairment. This allele is also a known risk factor for Alzheimer's disease (AD). [16,25,26,33]

Intraoperative factors affecting brain metabolism and homeostasis, such as hypotension, reduced cerebral perfusion, hypothermia, and depth of anesthesia, increase the risk of POCD. Research investigating the type and duration of surgery and anesthesia in relation to POCD risk has produced inconsistent findings. However, inhalation anesthesia is generally considered to present a higher risk of POCD than intravenous anesthesia.[16,30,31]

The postoperative environment is a crucial modifiable factor, with conditions such as sleep disturbances, unfamiliar surroundings, pain, and complications such as infection and delirium increasing the risk of cognitive impairment. POD may progress to long-term cognitive impairment and is associated with adverse outcomes, including a decline in activities of daily living (ADL) and increased mortality.[30,31,33]

Diagnosis and biomarkers for POCD

POCD requires both preoperative and postoperative evaluations to detect any cognitive decline. Existing diagnostic methods employ cut-offs that compare results to the patient's baseline or a reliable change index (RCI) derived from a control group, utilizing percentages, standard deviation calculations, and z-scores.[5,10] Generally, POCD is diagnosed when there is a decline in at least two tests or parameters of cognitive function. The diagnostic threshold varies but is typically set at higher than two standard deviations using the Z-score method or a 20% decline from baseline.[12,34] Baseline assessment was conducted one week prior to surgery, with subsequent evaluations of cognitive function using neuropsychiatric tests optimally performed at one week, three months, and 12 months after surgery.[5,10] Neuropsychiatric evaluations should be conducted after the resolution of acute care and surgical problems. To date, no specific test has been developed for the detection of POCD. Commonly employed neuropsychiatric assessments include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Addenbrooke's Cognitive Examination III, and Quick Mild Cognitive Impairment Screening.[34]

Currently, no biological or radiological markers are available to confirm the diagnosis of POCD. Diagnosis relies on neuropsychiatric examinations. Given that POCD is attributed to neuroinflammation, various molecular markers measured in the serum and cerebrospinal fluid (CSF) have been investigated as predictors and for the risk stratification of POCD. Inflammatory biomarkers, such as IL-6, TNF-α, CRP, and HMGB1, and neuronal injury markers, such as S100β, amyloid beta, and neuron-specific enolase (NSE), have shown promise in predicting POCD.[11,16] Although CSF biomarker testing is considered superior, its clinical application is limited.[20] MicroRNAs (miRNAs), particularly miR-29, are associated with several neurodegenerative disorders. miR-291-3p is linked to hippocampal cell proliferation and is a potential diagnostic biomarker; however, further research is required to elucidate its role in the POCD pathway.[35]

Management of POCD

The management of POCD emphasizes preventive strategies. Conducting a comprehensive preoperative assessment facilitates the identification of modifiable risk factors and serves as a preventive measure. In geriatric patients, perioperative assessment is crucial for the holistic evaluation of health status, including baseline cognitive function, as stated in several guidelines.[36,37] Comprehensive Geriatric Assessment (CGA) is an effective tool for systematically identifying medical, psychosocial, and functional limitations in elderly patients. It evaluates comorbidities, cardiorespiratory reserve, frailty, cognitive function, polypharmacy, and overall geriatric health, thereby providing a foundation for personalized perioperative care to meet specific needs.[16,38,39] The Enhanced Recovery After Surgery (ERAS) protocol, developed through various measures, encompasses preoperative, intraoperative, postoperative, and post-discharge care. This approach has demonstrated beneficial effects on postoperative recovery, including preservation of cognitive function.[37,38]

Enhancing cardiovascular fitness and nutrition and increasing brain activity through intellectual stimulation and education can bolster brain function and resilience in response to stress.[26,39] Cognitive training during the perioperative period is recommended; however, evidence supporting its effectiveness in terms of method, duration, and timing is limited.[40–43] Prehabilitation, which involves structured cognitive training, such as reading, writing, mental exercises, and compound cognitive activities prior to surgery, has shown positive outcomes, even

with simple exercise methods. These interventions can be delivered through computer- or non-computer-based programs in healthcare settings or at home. Cognitive training conducted during both the preoperative and postoperative periods has been shown to have beneficial effects.[40,41]

Physical exercise, including resistance training and aerobic activities, can enhance mitochondrial stability and energy metabolism, thereby reducing the risk of POCD.[16] One study reported that a preoperative physical activity intervention consisting of 40 min of daily aerobic exercise for 5–7 days before surgery positively influenced the preservation of cognitive function.[43] Optimizing nutritional status ensures an adequate supply of nutrients and provides anti-inflammatory and antioxidant benefits that contribute to cognitive recovery. An optimal diet can promote vagal anti-inflammatory activity and reduce lipopolysaccharide-induced NO release from astrocytes.[24]

Intraoperative adjustment may be necessary to maintain cerebral homeostasis and preserve cognitive function.[37] Minimally invasive laparoscopic surgical techniques typically induce less stress and tissue trauma. Regional anesthesia is generally preferred; however, when general anesthesia is required, agents with short half-lives and minimal neurotoxicity are recommended.[30,33] Intraoperative management of hemodynamics, cerebral perfusion, duration and depth of anesthesia, blood glucose levels, and body temperature is crucial, especially in vulnerable individuals, because hypotension, hypoxia, hypothermia, and hyperglycemia can exacerbate neuroinflammation and cognitive decline.[36,37,39] The use of EEG-based monitors, such as the bispectral index (BIS), is recommended to monitor anesthesia depth, thereby preventing over-sedation and minimizing cognitive side effects in high-risk patients.[16,35]

Rehabilitation programs tailored to patient capabilities can expedite recovery and enhance cognitive outcomes. Postoperative care emphasizes rehabilitation through cognitive exercises, early mobilization, and supportive care.[16,33] Continuous monitoring and follow-up with periodic cognitive function reassessments are vital. Preventing and detecting postoperative pulmonary complications, infections, and depression, which can impair cognitive function, is crucial.[30] POD poses a risk of long-term cognitive impairment and is associated with poor outcomes. Preventive measures for POD include identifying and treating infections, correcting anemia and electrolyte imbalances, managing pain, and addressing sleep disturbances.[36,39] The avoidance of potentially harmful medications, as outlined by the American Geriatrics Society (AGS) Beers criteria, is critical. This includes medications with central nervous system and cognitive effects, such as benzodiazepines, anticholinergics, antihistamines, and antipsychotics.[33,36] If cognitive impairment persists, long-term surveillance with multidisciplinary care is necessary.[11]

Pharmacological treatment of POCD

The involvement of neuroinflammation in the pathogenesis of POCD presents opportunities for identifying new therapeutic targets along inflammatory signaling pathways for its prevention and treatment.[24] Clinical trials have evaluated various agents with anti-inflammatory and neuroprotective properties to determine their efficacy in the treatment of POCD. Anti-inflammatory agents, such as minocycline and IL-1 receptor antagonists, along with neuroprotective agents, such as insulin-like growth factor 1 (IGF-1), are not recommended for POCD prevention or management because of insufficient supporting evidence and concerns regarding their efficacy and safety. Although certain neuroprotective agents, including melatonin and resveratrol, have demonstrated potential, their results have been confined in preclinical trials.[24,35] Evidence supporting the use of cholinergic agents, such as anticholinesterases and donepezil, still limited.[9]

Several agents have shown promising results and have been integrated into the care of high-risk patients. Dexmedetomidine, which is known for its anti-inflammatory effects, is recommended as a sedation option to prevent POD and POCD in at-risk patients.[22] The use of cyclooxygenase-2 (COX-2) inhibitors is recommended for short-term analgesia because of their benefits in preventing early POCD. Although dexamethasone has shown benefits in preclinical trials, its efficacy has not been demonstrated in randomized controlled trials (RCTs).[9,24] It is recommended for the management of postoperative nausea and vomiting (PONV).[9,11,39] The anti-amyloid beta/tau agent aducanumab is not recommended for POCD prevention because of safety concerns and clinical impracticality related to cost and safety monitoring. It shows delayed benefits for Alzheimer's disease, rendering it unsuitable for perioperative use.[11]

Conclusion

POCD is characterized by a decline in cognitive function after surgery. Its pathogenesis involves a neuroinflammatory process, with age-related changes in innate immunity and cellular senescence playing significant roles in exacerbating surgical stress inflammation. Risk factors include advanced age, lower educational attainment, ApoE4 carriage, and pre-existing MCI. Diagnosis is based on reassessment of cognitive function. As the understanding of disease pathogenesis has advanced, several potential biomarkers and

pharmacological targets have been identified. While the condition is transient, genetic predisposition and pre-existing cognitive impairment may affect prognosis, potentially leading to neurodegenerative diseases and highlighting the necessity for preventive strategies. CGA is crucial for identifying and addressing modifiable risk factors. Prehabilitation involving cognitive and physical training, and optimization of perioperative health status and modifiable risk factors are central in managing POCD. Although recommendations for the pharmacological treatment of POCD are limited, agents with anti-inflammatory properties, such as dexmedetomidine, dexamethasone, and COX-2 inhibitors, have been integrated into perioperative care.

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Conflict of Interest
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