JOURNAL

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Postoperative Cognitive Dysfunction in Craniotomy: Mechanisms, Challenges, and Future Directions

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OPEN ACCESS

NARRATIVE REVIEW

ARTICLE HISTORY

Received: March 1, 2025
Revised: May 3, 2025
Accepted: June 17, 2025

DOI: 10.61716/jnj.v3i2.

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Abstract

Background: Postoperative cognitive dysfunction (POCD) is a clinical concern that can affect patients undergoing craniotomy, often impairing memory, attention, and executive function. Despite advances in neurosurgical and anesthetic techniques, POCD remains prevalent and under-recognized. **Purpose:** This review aims to explore the underlying mechanisms and contributing factors of POCD in the context of craniotomy under general anesthesia. **Methods:** A narrative literature review method was employed to examine publications retrieved from major databases, including PubMed, Scopus, and ScienceDirect, between 2015 and 2025. Selected studies focused on adult patients and provided insights into both clinical manifestations and molecular pathways linked to POCD. **Results:** The analysis revealed that factors such as advanced age, duration of anesthesia, and neuroinflammatory responses significantly influence the development of POCD. Mitochondrial dysfunction and oxidative stress were frequently cited as key contributors to neuronal damage following surgery. **Conclusions:** In terms of clinical management, the literature suggests that early cognitive assessment and tailored anesthetic strategies may reduce the risk of long-term impairment. Although definitive treatment remains elusive, this review highlights the importance of early identification and multidisciplinary approaches to mitigate POCD in post-craniotomy patients. Future research should prioritize standardized diagnostic criteria and explore neuroprotective interventions to improve cognitive outcomes following neurosurgical procedures.

Keywords: anesthesia, general, cognition disorders, craniotomy, neuroinflammation, risk factors

Introduction

Postoperative cognitive dysfunction (POCD) has emerged as a critical and increasingly recognized complication of modern surgical practice, particularly in the aging global population (1). Defined as a measurable decline in cognitive performance following anesthesia and surgery, POCD encompasses impairments in memory, attention, executive function, and language fluency (2,3). While transient in some cases, POCD can persist for months or even years, profoundly affecting quality of life, functional independence, and long-term neurological outcomes (1).

Globally, the prevalence of POCD varies widely depending on surgical type, patient demographics, and assessment methodology. In general surgical populations, POCD has been reported in 17–43% of patients within the first month postoperatively, with 10–25% still affected at 3 to 6 months (4). Cardiovascular and orthopedic surgeries show particularly high rates, with up to 70% of patients experiencing POCD within one week following coronary artery bypass grafting (1). Among elderly individuals who represent a growing proportion of surgical candidates, the incidence is even more

pronounced, reaching 42.4% in some cohorts (5). These figures underscore POCD as a global public health concern, especially in regions with rapidly aging populations and expanding access to surgical care (6).

Despite this widespread impact, POCD remains underdiagnosed and underreported in neurosurgical contexts, particularly following craniotomy under general anesthesia (7). Craniotomy presents unique challenges: the direct manipulation of brain tissue, disruption of the blood-brain barrier, and exposure to neurotoxic agents all heighten the risk of cognitive sequelae (8–10). Yet, the true prevalence of POCD in this population is difficult to ascertain due to overlapping neurological symptoms, variability in postoperative assessment timing, and lack of standardized diagnostic criteria (11). Preliminary studies suggest that cognitive decline following craniotomy may be both more frequent and more persistent than previously appreciated, with some patients exhibiting deficits beyond one year postoperatively (12).

The novelty of this review lies in its focused exploration of POCD within the craniotomy population, a subgroup often overlooked in broader perioperative neurocognitive disorder research. By synthesizing current evidence on epidemiology, clinical presentation, and underlying mechanisms, this review aims to illuminate the distinct neurocognitive risks associated with craniotomy and advocate for improved screening, prevention, and management strategies tailored to neurosurgical patients

Methods

This study employed a narrative literature review design to explore the phenomenon of postoperative cognitive dysfunction (POCD) in patients undergoing craniotomy under general anesthesia. The review was conducted remotely in Purwokerto Timur, Central Java, Indonesia, over a period spanning from March to July 2025, utilizing reputable online databases such as PubMed, ScienceDirect, Scopus, and Google Scholar. No original data collection was performed; instead, the research focused on extracting and analyzing conceptual variables, including type and duration of anesthesia, patient age, and surgical approach as independent variables, with POCD incidence and severity as key outcomes.

The review targeted adult patient populations discussed in peer-reviewed literature, with purposive sampling applied to select studies published between 2011 and 2025, written in English, and directly addressing POCD in neurosurgical settings. Studies involving pediatric subjects or lacking peer review were excluded. Reference management and thematic coding were facilitated using Zotero and qualitative synthesis frameworks, enabling categorization of findings into epidemiological trends, mechanistic insights, and clinical implications. Although no physical instruments were used, the methodological rigor was upheld through systematic organization and critical appraisal of included sources. Ethical approval did not apply to this study due to its non-interventional nature; however, all selected publications were reviewed to ensure adherence to ethical standards, and a fit test of ethical compliance was performed by confirming that informed consent and institutional approval were obtained within each original study.

Results

Based on the findings from this narrative literature review, the results suggest that postoperative cognitive dysfunction (POCD) following craniotomy under general anesthesia is significantly influenced by several interrelated factors. The most frequently reported contributors

include advanced age, longer anesthesia duration, and pre-existing neurological vulnerabilities. Mechanistic insights drawn from the literature consistently point to neuroinflammation, oxidative stress, and mitochondrial dysfunction as key pathways disrupting neural function after surgery.

Clinical studies reviewed also revealed variability in cognitive outcomes depending on the assessment tools, timing of evaluations, and surgical complexity. Early postoperative cognitive changes were typically characterized by impairments in memory, attention, and executive function, with some patients experiencing prolonged cognitive decline. However, literature also highlighted promising mitigation strategies such as personalized anesthetic techniques, early neuropsychological assessment, and multidisciplinary care, all of which may help reduce the risk or severity of POCD.

Taken together, the review emphasizes that POCD remains an under-recognized complication with potentially significant impacts on postoperative recovery and quality of life. It underscores the need for standardized diagnostic criteria and further research into neuroprotective approaches that may improve outcomes for craniotomy patients.

Table 1. Ten pivotal studies examining postoperative cognitive dysfunction (POCD) in patients undergoing craniotomy under general anesthesia

Author(s)	Year	Topic	Purpose	Method	Result	Sample Size
Smith et al.	2024	Neuroinflammation in POCD	To explore anesthesia-induced neuroinflammatory mechanisms in POCD	Narrative review of molecular and clinical studies	Identified microglial activation and oxidative stress as key contributors	Not specified
Viderman et al.	2023	POCD after general vs. regional anesthesia	To compare cognitive outcomes between anesthesia types	Retrospective cohort analysis	General anesthesia associated with higher POCD incidence	3633 patients
Varpaei et al.	2024	Conceptual analysis of POCD	To define POCD and synthesize its attributes and risk factors	Literature-based concept analysis	Clarified POCD definitions and emphasized need for standardized criteria	86 articles
Evered et al.	2011	POCD independence from surgery type	To assess whether POCD is linked to anesthesia or surgery type	Prospective observational study	Found POCD independent of surgery type but related to anesthesia exposure	Not specified
Ballard et al.	2012	Optimized anesthesia to reduce POCD	To test if tailored anesthesia reduces POCD in older adults	Randomized controlled trial	Optimized anesthesia reduced POCD incidence and improved recovery	Not specified
Khan et al.	2025	POCD in TBI patients after extracranial	To assess cognitive outcomes in TBI patients	Meta-analysis of clinical studies	Highlighted increased POCD risk in TBI patients post-	5 studies

Author(s)	Year	Topic	Purpose	Method	Result	Sample Size
		surgery	under general anesthesia		surgery	
Aldin Varpaei et al.	2024	POCD prevalence and consequences	To analyze POCD definitions and its impact on quality of life	Systematic literature review	Found POCD significantly affects long-term cognitive and emotional health	6336 accesses
ISPOCD Investigators	1998	International POCD study	To assess POCD prevalence across countries and surgery types	Multinational prospective study	POCD occurred in 25.8% of patients at 1 week, 9.9% at 3 months post-op	>1000 patients
Silbert et al.	2014	POCD in elderly after major surgery	To investigate cognitive decline in elderly patients postoperatively	Longitudinal cohort study	Found persistent cognitive decline in elderly patients after surgery	300 patients
Rundshagen et al.	2014	POCD mechanisms and clinical relevance	To review the pathophysiology and clinical implications of POCD	Narrative literature review	Emphasized neuroinflammation and mitochondrial dysfunction as key factors	Literature review

The table presents a synthesis of ten pivotal studies examining postoperative cognitive dysfunction (POCD) in patients undergoing craniotomy under general anesthesia. Each entry outlines the study's author(s), year of publication, research topic, stated purpose, methodology, results, and sample size where available. The selected studies span observational cohorts, randomized controlled trials, systematic reviews, and conceptual analyses published between 2011 and 2025.

This compilation highlights the multidisciplinary nature of POCD research, encompassing both clinical outcomes and mechanistic insights such as neuroinflammation, anesthetic effects, and cognitive assessment frameworks. Collectively, the table provides a comparative overview that underscores the variability in study design, diagnostic approach, and reported prevalence, serving as a foundational reference for understanding current evidence and identifying gaps in neurosurgical cognitive research.

Discussion

Postoperative cognitive dysfunction (POCD) following craniotomy under general anesthesia is increasingly recognized as a complex neurocognitive complication with profound implications for patient recovery and long-term quality of life (13). Unlike other surgical populations, neurosurgical patients face unique vulnerabilities due to direct manipulation of brain tissue, prolonged anesthesia exposure, and pre-existing neurological conditions (14–16). Recent studies estimate POCD prevalence in neurosurgical cohorts to range from 10% to 54% within the first few weeks, with persistent symptoms in up to 17% at three months postoperatively (17).

The pathophysiology of POCD is multifactorial, with neuroinflammation

emerging as a central driver (18). Surgical trauma activates systemic inflammatory responses that breach the blood-brain barrier, triggering microglial activation, cytokine release, and synaptic disruption, particularly in the hippocampus (7). Studies have identified NLRP3 inflammasome activation, oxidative stress, and mitochondrial dysfunction as key contributors to neuronal injury and cognitive decline (19–22). Moreover, epigenetic modifications and gut microbiota dysbiosis have recently been implicated as upstream modulators of neuroinflammatory cascades (23–25).

Distinguishing POCD from postoperative delirium (POD) remains a clinical challenge due to overlapping symptoms such as attention deficits and disorientation (26,27). However, POCD typically follows a delayed and insidious trajectory, manifesting days to weeks after surgery and persisting for months (1,2,28). POD, in contrast, is acute and fluctuating, often resolving within days. Despite these distinctions, both conditions share common risk factors and inflammatory pathways, suggesting a continuum of perioperative neurocognitive disorders (PNDs) (11,29,30).

Traditional cognitive screening tools like the MMSE and MoCA lack sensitivity for detecting subtle executive dysfunction in neurosurgical patients. Recent efforts have focused on developing domain-specific neuropsychological batteries and identifying biomarkers such as IL-6, CRP, and NLR to enhance diagnostic precision (31). Intraoperative cognitive monitoring during awake craniotomy has also gained traction, allowing real-time mapping of higher-order functions and improving postoperative outcomes (19).

Clinical Implications

POCD is associated with prolonged hospital stays, functional decline, and increased mortality, particularly in elderly patients (1,32,33). Yet, it remains underprioritized in perioperative planning. Emerging evidence suggests that personalized anesthetic strategies, prehabilitation, and early cognitive rehabilitation may mitigate POCD risk11. Moreover, nurse-led postoperative care has shown promise in improving cognitive outcomes and reducing caregiver burden. Looking ahead, the journey to unravel and mitigate POCD after craniotomy calls for an ambitious and multidisciplinary roadmap. Emerging insights from recent neurobiological and clinical studies demand a pivot in research priorities from retrospective observation to proactive intervention. The pursuit of predictive biomarkers, such as inflammatory cytokines and neurofilament light chain proteins, offers a promising avenue for identifying at-risk individuals before cognitive decline sets in. Equally important is the refinement of cognitive assessment tools: longitudinal, domain-specific evaluations tailored for neurosurgical patients can provide a clearer window into the subtleties of recovery. Meanwhile, therapeutic innovation must shift toward neuroprotective strategies that address underlying molecular disruptions targeting inflammation, oxidative stress, and mitochondrial instability with precision medicine approaches.

Limitations

This literature review is limited by the absence of direct participant involvement and primary data collection, as the study design relied solely on previously published articles. Consequently, variability in sample sizes, intervention methods, and postoperative cognitive assessments

across studies made comparative analysis challenging. The selected literature spanned diverse clinical settings and surgical techniques, which may affect the generalizability of findings specific to craniotomy patients. Additionally, data collection occurred over a relatively short period (March to July 2025), and the scope was restricted to publications available in English from major electronic databases.

Some studies lacked consistent definitions or standardized tools for assessing postoperative cognitive dysfunction, which could introduce interpretation bias during synthesis. While thematic coding was employed to analyze core mechanisms and outcomes, the qualitative nature of this approach may limit statistical inference. Future research should aim to incorporate longitudinal clinical trials with larger neurosurgical cohorts, utilize harmonized cognitive screening protocols, and explore biomarker-guided interventions to strengthen the precision and applicability of POCD management strategies.

Conclusion

In the evolving landscape of neurosurgery, postoperative cognitive dysfunction (POCD) has emerged as a critical, yet often overlooked, dimension of patient care. This review has highlighted the unique vulnerability of craniotomy patients not merely due to the technical complexity of brain surgery, but because of the profound neurobiological processes it unleashes. From inflammation and oxidative stress to diagnostic ambiguity and limited therapeutic options, POCD challenges both the clinician's intuition and the system's preparedness. Yet, within this complexity lies opportunity. By embracing cognition as an essential surgical outcome, neurosurgical teams can redefine recovery not just by survival or neurological stability, but by the restoration of identity, autonomy, and mental resilience. Looking forward, a convergence of personalized medicine, targeted neuroprotection, and long-term cognitive monitoring holds the promise of transforming how we safeguard the brain during and after surgery. Through collaboration, innovation, and continued inquiry, the goal is not only to heal but to preserve and empower the very essence of what makes us human.

Acknowledgement

The completion of this review would not have been possible without the unwavering support and contributions of many individuals and institutions. I would like to express my deepest gratitude to my academic advisor, whose expertise, insight, and guidance shaped the trajectory of this work from its earliest stages. I am also indebted to the faculty and staff at Universitas Harapan Bangsa for providing the academic environment and resources necessary to pursue this research. Special appreciation goes to my peers and collaborators, whose thoughtful dialogue and shared commitment to inquiry enriched the discussion and broadened its relevance. Additionally, I extend my thanks to the patients and clinical staff whose real-world experiences and perspectives reminded me of the human impact behind the data. Finally, I am grateful to my family and friends for their encouragement, patience, and belief in the value of this work. Their support has been a quiet, constant force, making all the difference throughout this journey.

Funding

None

Conflict of Interest

The authors have confirmed that they have no competing interests

Data Availability

The datasets and materials generated and analyzed during the current study are available from the corresponding author upon reasonable request. All relevant data have been included in the manuscript or supplementary information files, where applicable. Access restrictions may apply to proprietary or confidential data, but efforts will be made to share anonymized data in accordance with ethical and legal considerations.

Authors' Contributions

Awal Tunis Yantoro conceptualized the study framework, guided the development of the research objectives, and provided critical supervision throughout the manuscript preparation. Anton Suhendro led the literature search and screening process, contributed to data extraction, and assisted with organizing the review structure. Indri Wijayanti focused on synthesizing the pathophysiological mechanisms and interpreting clinical relevance across studies, ensuring the biological accuracy of the discussion section. Made Suandika contributed to drafting the manuscript, integrating thematic coding results, and harmonizing the narrative flow across all sections. Rahmaya Nova Handayani provided support in formatting, referencing, and technical editing, as well as maintaining quality control throughout the writing process. Dwi Agus Yulianto was responsible for the final manuscript review, contributed to data validation, and coordinated communication among all team members. Yuniar Melissa Kisdyanti contributed to drafting the manuscript and final version to the Journal. All authors reviewed and approved the final version of the manuscript for publication.

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