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Postoperative Delirium and its Potential Predisposition to Chronic Dementia: A Review

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Abstract
Postoperative delirium (POD) is a multifaceted condition characterized by disturbances in attention, awareness and cognition, commonly occurring after surgical procedures. It involves a complex interplay of predisposing factors such as advanced age, preexisting comorbidities and preoperative cognitive impairment. Additionally, precipitating factors like surgery-induced stress, pain and the use of certain medications, along with perpetuating factors such as electrolyte imbalances and sleep disturbances, contribute to its onset and progression. This review comprehensively examines the intricate relationship between POD and the subsequent development of chronic dementia, highlighting recent research findings and offering new insights into the mechanisms underlying this association. The implications of these findings for clinical practice and future research directions are also discussed, underscoring the critical importance of early identification and management of POD to potentially mitigate the risk of long-term cognitive decline.

INTRODUCTION

Postoperative delirium (POD) is a critical neuropsychiatric condition characterized by significant disturbances in attention, awareness and perception. These disturbances are often accompanied by disorientation, agitation, hallucinations and a range of other behavioral abnormalities. The hallmark features of POD include fluctuating levels of consciousness and disorganized thinking, which can significantly impair a patient's ability to interact with their environment and respond to stimuli appropriately. This condition not only poses immediate risks to patient safety but also complicates postoperative recovery and prolongs hospital stays.

In contrast, postoperative cognitive decline (POCD) encompasses a broader spectrum of cognitive deficits. These deficits include impairments in memory, executive function, processing speed, and visuospatial abilities. POCD is typically identified through comprehensive neuropsychological testing, which can detect subtle changes in cognitive function that may not be immediately apparent. While POCD is generally milder than delirium, its impact on daily functioning and quality of life can be profound, affecting the ability to perform routine tasks, maintain independence and engage in social activities[1].

The diagnosis of delirium involves the use of various validated tools, such as the Confusion Assessment Method (CAM) and the Delirium Rating Scale (DRS), which assist clinicians in accurately identifying and assessing the severity of the condition. These tools are essential for ensuring timely and appropriate intervention, which can mitigate the adverse outcomes associated with POD[2].

Research has shown that baseline conditions such as formal dementia or the presence of neuropsychiatric symptoms can significantly increase the risk of developing POD in surgical patients. For instance, individuals with preexisting cognitive impairments or psychiatric disorders are more susceptible to the cognitive and neurochemical disruptions that precipitate delirium[3]. However, the reverse relationship, where POD potentially increases the risk or severity of long-term dementia, remains a crucial area of investigation. Understanding this relationship could have significant implications for the management and prevention of dementia in postoperative patients, necessitating further research to elucidate the underlying mechanisms and long-term outcomes[4].

Potential Pathophysiology

Surgical Anesthesia: Inhaled anesthetics have been shown to enhance the oligomerization and cytotoxicity of peptides associated with Alzheimer's disease, contributing to neurodegenerative processes[5]. Specific anesthetic agents, including volatile anesthetics like isoflurane and sevoflurane, as well as intravenous agents such as propofol, have been implicated in inducing neurotoxicity and cognitive dysfunction in both animal models and human studies[6]. Isoflurane and desflurane, in particular, induce Abeta oligomerization by causing chemical shift changes in critical amino acid residues (G29, A30 and I31), reinforcing the hypothesis that these anesthetics may accelerate the onset of Alzheimer's disease[7]. The neurotoxic effects of anesthetic agents can vary significantly depending on factors such as dose, duration of exposure and individual susceptibility, highlighting the importance of personalized anesthesia management for patients, especially those with dementia or at risk of cognitive impairment[8].

Research by Palotas *et al.* demonstrated that cerebrospinal fluid (CSF) tau and amyloid ß levels changed from normal to patterns consistent with mild cognitive impairment (MCI) six months after coronary artery bypass graft (CABG) surgery[9]. Similarly, Tang et al. found that even minor surgery could cause the CSF tau/amyloid ß ratio to shift towards an Alzheimer's pattern within 48 hours post-surgery, accompanied by increased levels of pro-inflammatory cytokines such as Interleukin-6 (IL-6)[10]. Further supporting these findings, Kline *et al.* reported a decrease in cortical and hippocampal gray matter volume by about 10% six months after surgery, suggesting significant structural changes in the brain[11]. These studies collectively indicate that surgical procedures may exacerbate the neuropathological processes underlying Alzheimer's disease, although the condition of the brain at the time of surgery plays a crucial role in determining the outcome[12].

Postoperative Analgesia: The use of opioids for postoperative analgesia is a double-edged sword, as opioid-induced respiratory depression and sedation can lead to hypoxia and cerebral hypoperfusion, thereby exacerbating cognitive impairment and increasing the risk of delirium in vulnerable patients[13]. Inadequate pain management is another critical factor, as it can lead to fragmented sleep and sleep deprivation, both of which are well-established risk factors for delirium[14]. Furthermore, patients with preexisting cognitive impairments or comorbidities such as dementia and depression are at an elevated risk of delirium when exposed to analgesic medications[15].

A systematic review identified six studies comparing the effects of different opioid analgesics on postoperative delirium and cognitive decline, as well as five studies comparing intravenous and epidural routes

of administering analgesia. The review consistently found that meperidine was associated with an increased risk of delirium in elderly surgical patients. However, no significant differences in postoperative delirium or cognitive decline were observed among other commonly used opioids such as morphine, fentanyl, or hydromorphone, suggesting that the choice of opioid might be less critical than other factors such as dosing and patient susceptibility[16,17].

Postoperative Complications: Postoperative complications, including delirium, stroke, myocardial infarction and systemic infections, have been independently associated with an elevated risk of long-term cognitive impairment and dementia[18,19]. Acute respiratory distress syndrome (ARDS) exemplifies this risk, as up to 75% of survivors exhibit deficits in multiple neurocognitive domains six months after discharge, with improvements dropping to only 45% at one year and no significant progress observed up to five years later[20]. Sepsis presents a similar scenario, with cognitive dysfunction affecting up to 78% of survivors[21,22]. Additionally, studying non-fatal infective episodes, Dunn *et al.* found a significant association between incident dementia and more than two such episodes, suggesting a link between repeated infections and cognitive decline[23].

Neuroinflammation: Surgical procedures trigger a systemic inflammatory response characterized by the release of pro-inflammatory cytokines and activation of immune cells, leading to neuroinflammation and potential neuronal injury in susceptible individuals[24]. Prolonged or severe surgical stress can exacerbate these neuroinflammatory processes, contributing to neurodegeneration and increasing the risk of long-term cognitive decline and dementia[25].

Vascular Impairment: Postoperative complications such as stroke and myocardial infarction contribute to cerebrovascular pathology and vascular cognitive impairment. These conditions represent significant risk factors for both vascular dementia and Alzheimer's disease[19]. To mitigate the risk of postoperative cognitive decline and dementia, perioperative management strategies must focus on reducing the incidence and severity of vascular events and optimizing cerebral perfusion in at-risk patients[18].

RESULTS AND DISCUSSIONS

Cholinergic Deficiency Hypothesis in Delirium: A Synthesis of Current Evidence: The cholinergic deficiency hypothesis posits that delirium is linked to substances that impair cholinergic function, such as toxins and certain medications. Recent evidence from epidemiological studies and anticholinergic assays has provided robust support for this hypothesis. Patients who have higher exposure to medications with anticholinergic effects tend to experience more severe cases of delirium, indicating a clear connection between cholinergic dysfunction and the severity of delirium symptoms[26].

This hypothesis, extensively researched in the context of Alzheimer's disease (AD), offers valuable insights into the pathophysiology of delirium. Alzheimer's disease is characterized by a central cholinergic deficiency, evident in postmortem and in vivo studies. This deficiency is manifested through mechanisms such as decreased choline acetyltransferase (ChAT) activity and altered receptor densities. The degeneration of cholinergic neurons is central to the pathology of Alzheimer's disease, and similar dysfunctions are thought to contribute to the development of delirium. Thus, delirium and Alzheimer's disease may represent different points on a continuum of cognitive disorders rather than entirely distinct conditions[26].

The frequent confusion between the symptoms of delirium and dementia often leads to the underutilization of treatments specifically targeted at delirium. This is particularly problematic with hypoactive delirium, which is less obvious and thus more likely to be overlooked[27]. Delirium and dementia, both being organic mental disorders, frequently co-occur and share several clinical and neurological similarities. Individuals with one condition are at an increased risk of developing the other, suggesting a bidirectional relationship between these two disorders[28].

The hypothesis that postoperative delirium (POD) serves as a predisposing factor for dementia has garnered significant attention in the medical literature. Several studies support this hypothesis:

- **Fong *et al.* (2009):** This longitudinal study found that delirium was associated with an increased risk of cognitive decline and progression to dementia in patients with Alzheimer's disease. This study established a direct correlation between delirium and dementia, highlighting the impact of delirium on long-term cognitive health[30].
- **Davis *et al.* (2012):** A meta-analysis of prospective cohort studies demonstrated that individuals with a history of delirium had a significantly higher risk of developing dementia compared to those without a history of delirium. This finding underscores the long-term cognitive risks associated with delirium[29].
- **Fick *et al.* (2015):** This study showed that the association between delirium and dementia led to

increased hospital stays and significant functional decline. The study found that men were more likely to develop delirium and that an increase in dementia severity corresponded to a greater risk of delirium onset. These findings emphasize the compounded impact of delirium and dementia on patient outcomes[31].

- **Van Roessel *et al.* (2019):** This study found that patients with dementia had significantly lower functional and cognitive scores post-delirium and faced a higher risk of institutionalization. These results highlight the severe consequences of delirium in patients already suffering from dementia, further emphasizing the need for proactive management and prevention strategies[32].

These studies collectively underscore the significant relationship between POD and long-term dementia. They highlight the critical need for further research and improved perioperative care strategies to mitigate these risks. Understanding and addressing the factors that link POD with chronic dementia can lead to better patient outcomes and improved quality of life for those undergoing surgery.

CONCLUSION

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are significant complications that impact long-term cognitive health. The interplay of predisposing factors (age, comorbidities, preoperative cognitive impairment), precipitating factors (surgery stress, medications) and perpetuating factors (electrolyte imbalances, sleep disturbances) highlights their complexity. Research indicates that baseline dementia or neuropsychiatric symptoms increase the risk of POD and POD itself may exacerbate long-term cognitive decline and dementia. Anesthesia, particularly agents like isoflurane and sevoflurane and neuroinflammatory responses to surgery, further complicate these conditions. Effective perioperative management, including personalized anesthesia and vigilant postoperative care, is crucial. Continued research is essential to understand the mechanisms linking POD and dementia and to develop interventions to improve patient outcomes and quality of life. This underscores the importance of a multidisciplinary approach in perioperative care to address these multifactorial cognitive complications.

Recommendations: To mitigate the risks associated with postoperative delirium (POD) and postoperative cognitive decline (POCD), it is essential to adopt a comprehensive and multidisciplinary approach in perioperative care. Preoperative assessment should include thorough cognitive evaluations to identify patients at high risk. Personalized anesthesia protocols should be implemented, minimizing the use of agents like isoflurane and sevoflurane known to exacerbate cognitive impairment. Enhanced recovery protocols that emphasize adequate pain management, avoiding opioids when possible and promoting early mobilization and optimal sleep hygiene are crucial. Additionally, strategies to manage neuroinflammation, such as anti-inflammatory treatments, should be explored. Continuous education for healthcare providers on recognizing and managing delirium, along with family involvement in postoperative care, can also improve outcomes. Finally, further research into the mechanisms linking POD to long-term dementia is necessary to develop targeted interventions and refine perioperative practices, ultimately enhancing patient recovery and quality of life.

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