



Review Article

The Current State of Research on the Impact of Desflurane on Postoperative Delirium

Yong Liu* 

Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China

Abstract

Postoperative delirium (POD) is a common and severe postoperative complication, with its incidence in non-cardiac surgical patients ranging from 10% to 60% based on surgical types. POD is generally recognized as a result of the interaction between individual susceptibility and external inducing factors, in which anesthetic modes and drug selection play a crucial role for anesthesiologists. Most studies have indicated that inhalation anesthesia may raise the risk of POD compared with propofol-based intravenous anesthesia, yet such research mainly focuses on sevoflurane, with few exploring the differences among various inhaled anesthetics in relation to POD. Based on existing basic and clinical research, desflurane shows advantages over sevoflurane and isoflurane, as it causes less neuronal damage and milder neuroinflammatory responses, facilitates faster postoperative consciousness recovery, improves awakening quality and shortens extubation time in patients. However, the current evidence on the potential effects of desflurane on POD is insufficient to draw definitive conclusions. This review systematically summarizes the latest basic and clinical research on desflurane and POD, aiming to clarify the potential effects of desflurane on POD and explore its underlying mechanisms. More rigorously designed and precisely evaluated studies are urgently needed to further verify the efficacy of desflurane in POD prevention and provide evidence-based references for the rational selection of inhaled anesthetics in clinical practice.

Keywords

Postoperative Delirium, Desflurane, Inhaled Anesthetics, Neuroinflammation, Neuronal Damage, Perioperative Management

1. Introduction

Postoperative delirium (POD) is defined as an acute, usually transient cerebral dysfunction that typically occurs within the first week after surgery, with core clinical manifestations including impaired attention, fluctuating consciousness levels, and rapid cognitive decline. In November 2018, an international multidisciplinary expert panel revised the definition of POD and formulated more standardized clinical diagnostic criteria [1], which have since become the universal reference for clinical diagnosis and research evaluation of POD.

The incidence of POD varies significantly with surgical procedures and patient populations, and elderly patients are recognized as the core high-risk group. This phenomenon is closely linked to the continuous advancement of surgical and anesthetic techniques and the global aging trend, with over one-third of patients undergoing anesthesia and surgery currently aged 65 years or older. In China, the incidence of POD after cardiac surgery ranges from 5.5% to 46.0% [2, 3]; for elderly patients (≥ 65 years) undergoing non-cardiac surgery,

*Correspondence: Yong Liu (liuyong199707@163.com)

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the incidence is 6.1% to 57.1%, with an average of approximately 11.1%. POD incidence is notably higher in specific surgical types: 57.1% for neurosurgery, 18.1% for upper abdominal general surgery, 16.3% for thoracic surgery, and 15.2% for spinal and joint orthopedic surgery [4]. Globally, the overall POD incidence in elderly non-cardiac surgical patients is reported to be 10% to 60%, and 5% to 50% for cardiac surgical patients—an incidence range consistent with Chinese data, though regional differences exist due to factors such as medical resource allocation and perioperative management strategies. The wide variability in reported POD incidence is primarily attributed to three core factors: inconsistent diagnostic criteria and assessment time points across studies, differences in patient baseline characteristics (e.g., age, cognitive status, comorbidities), and variations in perioperative management protocols (e.g., anesthetic regimens, analgesic strategies, postoperative care). Risk stratification for POD can be primarily based on age, with elderly patients (≥ 65 years) as the high-risk group, and further stratified by surgical type—neurosurgery and cardiac surgery are classified as high-risk procedures, while minor superficial surgery is a low-risk category.

As a clinically consequential complication, POD significantly increases the risk of subsequent postoperative adverse events, including prolonged hospital stay, higher medical costs, increased reoperation rates, intensive care unit (ICU) admission, and unplanned 30-day readmission. These outcomes not only impair the quality and trajectory of patients' postoperative recovery but also exacerbate the economic burden on societal healthcare resources. From a long-term perspective, POD is also associated with an increased risk of persistent cognitive impairment and reduced long-term survival in elderly patients, further highlighting its clinical and socioeconomic impact.

Although the exact pathophysiological mechanisms of POD remain incompletely elucidated, accumulating evidence points to a complex interplay of intraoperative physiological stress, abnormal immune system activation, and systemic neuroinflammatory cascades as core pathogenic factors. Immune activation triggers the massive release of proinflammatory cytokines (e.g., IL-6, IL-1 β , TNF- α), which disrupt the blood-brain barrier's integrity, allowing peripheral inflammatory factors to infiltrate the central nervous system and induce central neuroinflammation. This neuroinflammation further leads to neurotransmitter imbalance (e.g., decreased acetylcholine, increased dopamine and norepinephrine) and oxidative stress damage to neurons, ultimately resulting in impaired cerebral function and the onset of POD. Additionally, cerebral structural abnormalities (e.g., atrophy, white matter lesions) in elderly patients may reduce cerebral adaptive capacity, making them more susceptible to POD induced by the above pathological processes.

In the absence of universally accepted and effective specific prophylaxis for POD, optimizing perioperative management strategies to reduce its incidence and severity has become a key clinical priority for anesthesiologists. Anesthetic modes

and drug selection are important modifiable factors in perioperative management: most studies suggest that inhalation anesthesia may carry a higher POD risk than propofol-based intravenous anesthesia, but existing research primarily contrasts sevoflurane with intravenous anesthesia, with few studies investigating the differential effects of various inhaled anesthetics on POD. Desflurane, a commonly used inhaled anesthetic, has unique pharmacokinetic properties (e.g., low tissue solubility, rapid elimination) and has been shown in basic studies to cause less neuronal damage and neuroinflammation than sevoflurane and isoflurane. However, clinical evidence on whether desflurane can reduce POD incidence or alleviate its severity remains conflicting and insufficient, and there is a lack of systematic analysis of its potential protective mechanisms and clinical application value. This constitutes the key knowledge gap addressed in the present review: by systematically summarizing the latest basic and clinical research on desflurane and POD, this study aims to clarify the potential effects of desflurane on POD, explore its underlying mechanisms, and provide evidence-based references for the rational selection of inhaled anesthetics in clinical practice for POD prevention.

2. Etiology and Prevention of Postoperative Delirium

2.1. Etiology of Postoperative Delirium

It is currently well-recognized that delirium is not triggered by a single factor but arises from the complex interaction of multiple predisposing and precipitating factors [5, 6]. Specifically, individuals with various vulnerable conditions—including advanced age, impaired cognitive function, severe physical illness or organ dysfunction, sensory deficits, malnutrition, frailty, electrolyte disturbances, drug or alcohol dependence, and smoking—exhibit reduced cerebral adaptive capacity. When these predisposing factors coexist with external precipitants (e.g., surgery, accidental injury, major life changes, extreme fatigue, sleep deprivation, inadequate or excessive sensory stimulation, intimidating or monotonous environments, and withdrawal symptoms), the risk of POD is significantly elevated. Additionally, several therapeutic agents, including analgesics, anticholinergics, benzodiazepines, antipsychotics, antidepressants, central nervous system stimulants, and corticosteroids, have been identified as potential triggers of POD [7].

2.2. Etiopathogenic Mechanisms of Postoperative Delirium

To date, the exact pathophysiological mechanisms underlying POD remain incompletely elucidated; however, research has primarily focused on several key theoretical hypotheses. The neuroinflammatory factor theory proposes that elevated

plasma concentrations of inflammatory markers (e.g., C-reactive protein, CRP) in patients with delirium may activate the coagulation pathway, reduce cerebral blood flow, and subsequently induce cerebral hypoxia and neuronal apoptosis, ultimately contributing to the development of POD [8]. The neurotransmitter imbalance theory, another prominent hypothesis, highlights the role of disrupted acetylcholine and dopamine homeostasis in POD pathogenesis. Specifically, decreased acetylcholine levels accompanied by increased dopamine and norepinephrine levels are thought to trigger delirium symptoms. Certain medications, such as anticholinergics and dopaminergic drugs, may exacerbate the risk of POD by interfering with these neurotransmitter systems [9]. Furthermore, the brain function alteration theory, supported by neuroimaging techniques (e.g., functional magnetic resonance imaging, fMRI), has demonstrated cerebral atrophy and white matter structural changes in patients with delirium. These structural abnormalities are associated with the duration of delirium and, particularly in elderly surgical patients, correlate with the incidence of POD.

2.3. Potential Mechanisms Underlying Desflurane-induced Effects on Postoperative Delirium

Based on etiological studies of POD, early laboratory investigations have revealed the differential effects of various inhaled anesthetics on inflammatory mediator responses. Notably, rodent studies have shown that isoflurane upregulates the expression of inflammatory mediators (e.g., IL-6, IL-1 β , TNF- α) in neurons [10]. A comparative study by Zheng et al. demonstrated that hippocampal IL-1 β levels were significantly higher two weeks postoperatively in mice treated with 1.8% isoflurane or 2.5% sevoflurane compared to those exposed to 10% desflurane, with concurrent impairments in memory and learning behavioral tests [11]. Another murine study observed that 2-hour exposure to 9% desflurane did not increase the cerebral expression of IL-6 or TNF- α and had no adverse effects on cognitive or behavioral functions, whereas equipotent sevoflurane (3% for 2 hours) induced significant impairments [12].

Inhaled anesthetics may also influence POD pathogenesis by regulating the differential expression of neurotransmitters. Studies in healthy human volunteers have shown that inhalation of high-concentration desflurane (>1.5 MAC) induces transient sympathetic nervous system activation, as reflected by increased plasma catecholamine levels and enhanced sympathomimetic effects (e.g., elevated blood pressure and heart rate). These effects are more pronounced in both intensity and duration than those observed with equipotent doses of isoflurane [13, 14]. Based on these findings, desflurane may exert less neuronal damage compared to other inhaled anesthetics, a property that may contribute to its lower incidence and severity of POD.

Different inhaled anesthetics exhibit varying degrees of

neurotoxicity, which may affect neuronal apoptosis and cerebral function. Biomarkers associated with Alzheimer's disease, such as β -amyloid (A β) and tau protein, are thought to play a role in POD pathogenesis. High concentrations of A β exert long-term neurotoxic effects, triggering neuronal death, cerebral dysfunction, and degeneration of ventricular, frontal lobe, and white matter structures, thereby potentially inducing POD. Multiple basic laboratory studies have shown that, compared to sevoflurane or isoflurane, desflurane is less likely to significantly increase A β accumulation, excessive tau phosphorylation, or caspase-3 activation (a key mediator of apoptosis) in neurons or brain tissue [15-17]. Desflurane is characterized by high chemical stability and low tissue solubility, with a blood/gas partition coefficient of 0.42—markedly lower than that of other inhaled anesthetics. This property enables its rapid elimination from the body, resulting in fast onset, rapid emergence, minimal accumulation, and controllable anesthetic effects, with no significant prolongation of elimination time following prolonged administration [3]. In vitro experiments have demonstrated that even high-concentration desflurane (12% for 6 hours) does not significantly increase A β concentrations [18]. A study by Zhang et al. [19] compared the effects of desflurane combined with epidural anesthesia versus other inhaled anesthetics on cerebrospinal fluid (CSF) levels of A β , tau protein, and other cognition-related proteins before and after surgery. The results showed that isoflurane increased CSF A β levels, whereas desflurane reduced postoperative CSF A β 42 concentrations—a key marker of neurocognitive function—within 2 hours after surgery.

2.4. Prevention and Treatment of Postoperative Delirium

Strategies for the prevention and treatment of POD should comprehensively consider individual susceptibility and potential precipitating risks, implement integrated management throughout the perioperative period (from preoperative preparation to postoperative recovery), and require collaboration between medical staff and patients' families. In clinical practice, prioritizing POD prevention is crucial: validated assessment tools should be used to identify preoperative risk factors, and timely interventions should be provided to patients with preexisting delirium or cognitive impairment. The Chinese Expert Consensus on the Prevention and Treatment of Postoperative Delirium in Elderly Patients (2023 Edition) details the recommendation levels and evidence bases for various interventions, emphasizes the importance of interdisciplinary teamwork, and recommends perioperative comprehensive intervention plans (including non-pharmacological strategies) for high-risk elderly patients to reduce the incidence and severity of POD. Notably, the consensus discourages the use of antipsychotics (e.g., haloperidol) for POD prevention and adopts a cautious approach to ketamine monotherapy, while suggesting potential benefits of combined ketamine and dexmedetomidine administration. Additionally, it highlights the

importance of strict intraoperative monitoring and management of the circulatory system in elderly patients, as well as the rational use of cardiovascular active agents to avoid hypotension or blood pressure fluctuations during anesthesia—all of which are supported by the highest levels of evidence and recommendation.

3. Research Status of the Association Between Desflurane and Postoperative Delirium

In 2020, a meta-analysis published in the *Journal of Clinical Anesthesia* comprehensively evaluated 39 randomized controlled trials (RCTs) involving 5,991 patients to assess the efficacy of various anesthetics in preventing POD following general anesthesia [20]. The study found that desflurane exhibited modest advantages over sevoflurane and midazolam in reducing the incidence of POD but showed no statistically significant difference compared to propofol or placebo. Furthermore, desflurane was less effective than dexmedetomidine and ketamine. The meta-analysis also reported odds ratios (OR) and 95% confidence intervals (CI) for each agent: desflurane (OR 3.81, 95% CI 1.08–13.43), sevoflurane (OR 5.62, 95% CI 2.00–15.80), and dexmedetomidine (OR 0.44, 95% CI 0.30–0.64), which was associated with a reduced risk of POD. Subgroup analysis further revealed no statistically significant differences in the incidence of POD among propofol, sevoflurane, and desflurane when used as the primary anesthetic. Additionally, a 2017 study published in the *Journal of Clinical Anesthesia* compared desflurane and propofol for POD prevention in 96 elderly obese patients undergoing total knee arthroplasty, with no significant differences between the two groups [21].

Recent studies have reported contrasting findings. A 2023 article published in *Frontiers in Aging Neuroscience* demonstrated a stronger association between desflurane use and POD in elderly patients, with an incidence rate of 25.4%—exceeding that of propofol (12.9%) and sevoflurane (16.2%) [22]. Specifically, patients anesthetized with desflurane had a 1.8-fold higher risk of developing POD compared to those receiving propofol (OR 1.766, 95% CI 1.049–2.974, $p=0.032$), whereas no difference was observed between the propofol and sevoflurane groups. The study also noted a longer duration of burst suppression in the propofol group compared to the desflurane and sevoflurane groups, with an association between the burst suppression rate and POD incidence that was inconsistent with previous findings [23]. Importantly, this study was a secondary analysis of secondary outcomes from prior experiments, which may introduce potential biases. Another study, published in *Acta Anaesthesiol Scand* in 2019 [24], conducted a secondary analysis of a prospective cohort involving 532 elderly surgical patients (mean age 73.5 years). The overall incidence of POD within the first two postoperative days was 41%, with a POD rate of 45% in patients receiving desflurane. Although this rate was higher than that in the sevoflurane

group, the difference was not statistically significant. The larger sample size in the desflurane group and the presence of multiple confounding factors limit the clinical applicability of these findings. Collectively, current evidence does not definitively confirm whether desflurane is more effective than other inhaled anesthetics in preventing POD.

4. Conclusions

In summary, current research does not definitively establish that desflurane is superior to other inhaled anesthetics in reducing the risk of POD. While basic and animal studies suggest that desflurane may have advantages in reducing neuronal damage compared to sevoflurane and other anesthetics, these findings have not been fully validated in clinical practice. Clinically, desflurane has been consistently associated with faster extubation and improved postoperative recovery when used for anesthetic maintenance. To further elucidate the potential effects of desflurane on POD, well-designed RCTs with larger sample sizes and longer follow-up periods are warranted to provide more conclusive evidence.

Abbreviations

POD	Postoperative Delirium
ICU	Intensive Care Unit
RCTs	Randomized Controlled Trials
CI	Confidence Intervals

Author Contributions

Yong Liu: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing

Conflicts of Interest

The author declares no conflicts of interest.

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Biography



Liu Yong is a physician in the Department of Anesthesiology at West China Hospital, Sichuan University. Dr. Liu received his Bachelor of Medicine degree from Xi'an Jiaotong University in 2020. He completed his standardized residency training in anesthesiology at West China Hospital, Sichuan University, in 2023. His current research interests focus on perioperative neurocognitive disorders and clinical anesthesiology.

Research Field

Liu Yong: research field perioperative neurocognitive disorders, research field local anesthetic toxicity, research field nerve block, research field perioperative lung protection strategies, and research field clinical anesthesiology.