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Narrative Review

The Potential Role of Ketamine in Preventing Delirium among Critically Ill Patients Following Coronary Artery Bypass Grafting: A Review

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Abstract

Introduction: Coronary artery bypass grafting (CABG) remains a cornerstone procedure in cardiovascular medicine; however, postoperative delirium is a frequent and serious complication, particularly among critically ill patients in the intensive care unit. Ketamine, known for its analgesic and N-methyl-D-aspartate (NMDA) receptor–modulating properties, has been proposed as a potential agent to reduce the incidence of delirium following cardiac surgery.

Method: A review was conducted by searching reputable scientific databases for studies addressing postoperative delirium, cardiac surgery, coronary artery bypass grafting, and postoperative cognitive dysfunction. Relevant literature examining the relationship between ketamine administration and the incidence or severity of post-CABG delirium was identified, analyzed, and synthesized.

Result: Eight thematic areas were explored: definitions and diagnostic criteria of delirium; epidemiology of postoperative delirium; pathophysiological mechanisms; risk factors for post-cardiac surgery delirium; associations between pain control, sedation practices, and delirium; complications of delirium in the critical care setting; and the timing, dosage, and efficacy of ketamine administration during and after CABG.

Conclusion: Current evidence regarding ketamine's effectiveness in preventing postoperative delirium after CABG remains inconclusive, with studies reporting mixed outcomes. Further standardized, high-quality research is needed to clarify optimal dosing strategies, assess safety profiles, and determine ketamine's true role in delirium prevention among critically ill cardiac surgery patients.

Keywords: Ketamine, Coronary Artery Bypass Grafting, Postoperative Delirium, Critical Care.

Introduction

Cardiovascular disease remains a leading cause of morbidity and mortality, affecting approximately 17 million individuals in the United States [1]. Coronary artery bypass grafting (CABG) is a cornerstone surgical intervention that improves myocardial perfusion, cardiac function, and overall quality of life. However, postoperative complications—particularly delirium—continue to pose significant challenges, often prolonging intensive care unit (ICU) stays, increasing healthcare costs, and adversely impacting long-term outcomes.

Anesthetic management during CABG should aim to optimize hemodynamic stability and minimize postoperative complications. Nevertheless, adverse

effects can occur, and postoperative delirium represents one of the most serious concerns. Delirium is characterized by acute disturbances in attention, awareness, and cognition, and has been linked to increased morbidity, prolonged mechanical ventilation, and higher mortality rates [2–4]. Cognitive impairment is also common following cardiac surgery, with more than half of CABG patients exhibiting some degree of postoperative cognitive dysfunction [5].

Ketamine, an intravenous anesthetic with potent N-methyl-D-aspartate (NMDA) receptor antagonism and anti-inflammatory properties, has attracted attention as a potential agent for reducing postoperative delirium and improving cognitive outcomes. However, findings from clinical studies remain inconsistent, with some suggesting neuroprotective effects and others showing minimal or no benefit [6].

This narrative review aims to synthesize current evidence on postoperative delirium following cardiac surgery, with a particular focus on the role of ketamine in its prevention and management among critically ill patients undergoing CABG.

Methods

Search Strategy

A comprehensive literature search was conducted using Scopus, Web of Science, PubMed, Cochrane Library, and Google Scholar. Search terms were based on Medical Subject Headings (MeSH) and included: postoperative delirium, postoperative cognitive dysfunction, restlessness, ketamine, and coronary artery bypass surgery. Articles eligible for inclusion comprised clinical trials, reviews, systematic reviews, and meta-analyses, selected for methodological rigor, clinical relevance, and level of evidence. Publications in both English and Persian were reviewed. This narrative review summarizes key findings regarding postoperative delirium (POD) after cardiac surgery, focusing on its definition, pathophysiology, epidemiology, risk factors, and the effects of ketamine dose and timing on POD prevention.

A comprehensive synthesis of the literature on postoperative delirium and ketamine use in coronary artery bypass grafting (CABG) is presented in **Table 1**. The table summarizes key concepts related to the definition, epidemiology, pathophysiology, risk factors, and complications of postoperative delirium, alongside current evidence on ketamine's pharmacological mechanisms, dosing strategies, and clinical outcomes. This overview highlights the multifactorial nature of delirium and underscores the variability in study findings regarding ketamine's efficacy, reflecting differences in patient populations, dosing regimens, and perioperative conditions.

Results and discussion

Definition of Delirium

Delirium is an acute neuropsychiatric syndrome characterized by a sudden disturbance in attention, awareness, and cognition, reflecting global cerebral dysfunction. Its clinical manifestations often fluctuate in severity and include altered psychomotor activity, disrupted sleep–wake cycles, and emotional instability [7].

Three main subtypes are recognized: hyperactive, hypoactive, and mixed. Hypoactive delirium, marked by lethargy and reduced responsiveness, is the most common yet frequently underdiagnosed, often mistaken for depression. Hyperactive delirium presents with agitation, restlessness, and rapid speech, while mixed delirium alternates between these two states, posing diagnostic challenges [8].

Epidemiology of Postoperative Delirium

Delirium is common across medical settings, particularly in older adults, with an estimated 23% prevalence among hospitalized patients. Post-surgical incidence varies by procedure—ranging from single-digit rates in minor operations to 17–19% in high-risk cases. In the ICU, delirium affects approximately 31.8% of patients, reaching 50–70% among those mechanically ventilated. Following cardiac surgery, incidence rates range from 26% to 52% [9–11].

Inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP) contribute to blood–brain barrier disruption and cerebral edema formation. The relationship between hypothermia during cardiopulmonary bypass (CPB) and POD remains debated. Evidence suggests that normothermic CPB (37°C) reduces postoperative neurocognitive complications compared to mild hypothermia (32°C) [10]. Nonpulsatile CPB flow may impair endothelial function and provoke systemic inflammation [12–14.]

Risk factors for postoperative delirium include advanced age, cognitive impairment, psychiatric history, cerebrovascular disease, hypoxia, prolonged

ventilation, atrial fibrillation, and renal dysfunction [15]. Long-term consequences include higher mortality, persistent cognitive decline, falls, and reduced functional independence [16].

Pathophysiology of Delirium

The pathogenesis of delirium after cardiac surgery is multifactorial, involving microembolic phenomena, neurotransmitter imbalances, and inflammatory responses [17]. Hypoxia, oxidative stress, and neuroinflammation contribute to cholinergic deficiency and dopaminergic hyperactivity, leading to cognitive dysfunction [7,18].

Key neurotransmitter mechanisms include:

Acetylcholine deficiency, disrupting arousal and attention [19].

Dopamine excess, contributing to agitation and hallucinations [20,21].

GABAergic dysregulation, often due to sedative use [20].

Glutamate excitotoxicity, promoting neuronal apoptosis during systemic inflammation [20,22].

Glucocorticoid excess, especially cortisol, exacerbating hippocampal vulnerability [20,23].

Serotonergic imbalance, with both hypo- and hyperactivity implicated in delirium [24].

Risk Factors After Cardiac Surgery

Studies indicate that preoperative atrial fibrillation, low Mini-Mental State Examination scores (<27), prolonged surgical duration, and electrolyte imbalance independently increase delirium risk. Sleep disruption in the ICU is a major precipitant. Older age, lower educational attainment, and widowed status also correlate with higher delirium incidence [25].

While factors such as gender, diabetes, and smoking show inconsistent associations [26], hematocrit level may serve as an independent risk marker. The relationship between delirium and mortality appears age-dependent, with younger patients requiring stronger stressors (e.g., anesthesia, ischemia) to develop delirium, whereas elderly or post-stroke patients exhibit heightened baseline vulnerability [27].

Pain Management After CABG and Delirium

Pain and delirium share a bidirectional relationship: untreated pain can exacerbate delirium, while excessive analgesia may precipitate it [28–32]. After CABG, pain from sternotomy, chest tubes, and graft sites increases sympathetic activation and myocardial oxygen demand [30]. Effective pain control is therefore critical yet challenging.

Ketamine has been explored as an opioid-sparing adjunct, reducing postoperative opioid requirements by approximately 20% in some trials using S (+)-ketamine, though side effects were noted [34,35]. Despite mixed findings, ketamine remains a promising component of multimodal analgesia strategies aimed at minimizing opioid exposure in critical care recovery pathways.

Sedation After Cardiac Surgery and Delirium

Postoperative sedation aims to prevent cardiac stress and facilitate mechanical ventilation weaning. However, sedative choice strongly influences delirium risk. Benzodiazepines are associated with higher delirium rates, whereas non-benzodiazepine agents such as propofol and dexmedetomidine are preferred for ICU sedation [30,36].

Propofol allows faster awakening and extubation compared to midazolam, while dexmedetomidine demonstrates superior delirium prevention and hemodynamic stability in postoperative cardiac patients.

Complications of Postoperative Delirium

POD affects up to 50% of cardiac surgery patients [37] and is associated with substantial morbidity, mortality, and healthcare costs—adding an estimated $28,000 per case in adjusted U.S. dollars [38]. Consequences include prolonged hospitalization, mechanical ventilation, infections, and long-term cognitive decline [11, 39–41].

Hyperactive delirium increases the risk of unplanned extubation and device removal [8]. Delirium independently predicts long-term mortality and readmission, particularly in younger cohorts without prior cardiac events [27,40]. These outcomes underscore the need for continuous monitoring and preventive strategies in critically ill postoperative patients.

Table 1. Summary of Key Themes in the Relationship between Ketamine and Postoperative Delirium after Coronary Artery Bypass Grafting (CABG)

Thematic Area	Key Concepts and Findings	Clinical/Research Implications	References
Definition of Delirium	Acute neuropsychiatric syndrome marked by fluctuating disturbances in attention, awareness, and cognition; subtypes: hyperactive, hypoactive (most common, often missed), and mixed.	Early recognition of hypoactive forms critical for ICU management; standardized assessment tools (e.g., CAM-ICU) recommended.	(7–8)
Epidemiology	Affects 23% of hospitalized adults, 31.8% in ICU, 50–70% in mechanically ventilated patients; incidence 26–52% after cardiac surgery.	High prevalence underscores need for prevention protocols in cardiac critical care; monitoring during and after CPB is essential.	(9–11,15–16)
Pathophysiology	Multifactorial: inflammation, oxidative stress, neurotransmitter imbalance (↓ACh, ↑DA, GABA dysregulation, glutamate excitotoxicity, cortisol excess, serotonin imbalance).	Highlights rationale for NMDA modulation (ketamine) as a therapeutic avenue; anti-inflammatory and neuroprotective strategies warranted.	(17–24)
Risk Factors After Cardiac Surgery	Age, cognitive impairment, atrial fibrillation, prolonged surgery, electrolyte imbalance, sleep disruption, hypoxia, renal dysfunction.	Preoperative risk screening and intraoperative neuroprotection may reduce delirium burden.	(25–27)
Pain and Analgesia	Pain increases sympathetic drive and delirium risk; excessive opioid use also problematic. Ketamine may reduce opioid requirements by ~20%.	Supports use of multimodal analgesia with low-dose ketamine as opioid-sparing strategy in CABG.	(28–35)
Sedation Practices	Benzodiazepines linked to higher delirium rates; propofol and dexmedetomidine preferred for ICU sedation.	Choice of sedative crucial for delirium prevention; non-benzodiazepine regimens recommended in postoperative ICU care.	(30,36)
Complications of Delirium	Up to 50% incidence after CABG; increases mortality, mechanical ventilation time, infection risk, cost (+$28,000 per case).	Reinforces delirium as a modifiable outcome measure; justification for prevention-focused anesthetic and ICU protocols.	(37–41)
Ketamine Pharmacology & Mechanisms	Noncompetitive NMDA antagonist; modulates GABA and dopamine pathways; anti-inflammatory, sympathomimetic, and neuroprotective properties.	Mechanistic rationale supports perioperative use; potential for inflammation modulation and neuroprotection.	(6,41–45)
Dosage & Timing Evidence	- 0.5 mg/kg bolus reduced delirium and CRP. - Dual bolus (0.5 mg/kg pre-sternotomy & pre-pump) lowered agitation. - High-dose (1–2 mg/kg) showed no cognitive benefit. - Infusion (1 mg/kg/h) modest benefit in elderly. - Co-use with midazolam prevented psychosis.	Effectiveness appears dose-dependent and context-sensitive; standardized dosing regimens needed for reliable outcomes.	(46–50)

Ketamine: Pharmacology and Mechanisms

First introduced in 1964, ketamine is a noncompetitive NMDA receptor antagonist with additional activity on GABAergic and dopaminergic pathways [6,41]. Its rapid onset (within 30 seconds IV) and sympathomimetic, analgesic, and anti-inflammatory properties make it a versatile anesthetic.

Experimental studies demonstrate neuroprotective effects via inhibition of nitric oxide synthesis, reduction of ischemia-induced inflammation, and enhancement of

hippocampal neuroplasticity [42–45]. The S (+) enantiomer shows greater potency and may confer enhanced neuroregenerative potential.

Dosage, Timing, and Clinical Evidence in Cardiac Surgery

Clinical trials on ketamine during CABG reveal mixed results:

Low-dose bolus (0.5 mg/kg) during induction reduced POD incidence via anti-inflammatory mechanisms [46].

Dual bolus dosing (0.5 mg/kg pre-sternotomy and pre-pump) lowered agitation scores postoperatively [47].

Comparisons between ketamine (1–2 mg/kg) and propofol for induction found no difference in cognitive outcomes, though ketamine reduced vasopressor requirements [48].

In older patients (>65 years), intraoperative infusion (1 mg/kg/h) modestly reduced early POD but results were inconclusive [49].

Dosing at 0.5 mg/kg more effectively lowered CRP levels than 0.25 mg/kg, without psychomimetic side effects when co-administered with midazolam [50].

These findings indicate that ketamine's effects on delirium are dose-dependent and context-sensitive, potentially influenced by anesthetic combinations, patient risk profiles, and perioperative factors. Although ketamine shows promise in modulating neuroinflammation and preserving cerebral perfusion, standardized, multicenter trials are necessary to define optimal dosing, timing, and patient selection.

Conclusion

Current evidence regarding the use of ketamine in coronary artery bypass grafting (CABG) surgery remains inconsistent. While some studies report a reduction in postoperative delirium, others fail to demonstrate a significant effect. These discrepancies may reflect variations in dosage, timing of administration, concomitant anesthetic techniques, and patient characteristics.

Given ketamine's complex pharmacologic profile and its potential neuroprotective and anti-inflammatory properties, further standardized, high-quality clinical trials are essential to determine its optimal dosing strategy, safety parameters, and true efficacy in preventing postoperative delirium among critically ill cardiac surgery patients. The existing uncertainty surrounding ketamine's neuroprotective potential underscores the need for multicenter investigations employing uniform diagnostic criteria, consistent outcome measures, and rigorous methodological designs.

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Conflict of Interest Disclosures

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Authors' Contributions

All authors contributed to the design and draft of the research and data collection, accomplished the data analysis, revised the all data and wrote the text. All authors approve and read the text version final

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Not applicable.

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