Review Article

Current approach to diagnosis and treatment of delirium after cardiac surgery

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ABSTRACT

Delirium after cardiac surgery remains a common occurrence that results in significant short- and long-term morbidity and mortality. It continues to be underdiagnosed given its complex presentation and multifactorial etiology; however, its prevalence is increasing given the aging cardiac surgical population. This review highlights the perioperative risk factors, tools to assist in diagnosing delirium, and current pharmacological and nonpharmacological therapy options.

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INTRODUCTION

Delirium is a condition characterized by an acute cognitive decline, a fluctuating mental status, disturbance of consciousness, inattention, or disorganized thinking.[1] It is a well-recognized adverse prognostic marker in Intensive Care Unit (ICU) patients and is associated with increased morbidity, mortality, and the development of long-term neurocognitive deficits.[2,3] The incidence has been reported to occur between 16% and 73%[4-8] of patients after cardiac surgery; yet, cardiac surgeons, anesthesiologists, intensivists, and nurses may fail to recognize delirium in up to 84% of patients.[9,10] In this article, we review delirium after cardiac surgery including its perioperative risk factors, tools to assist in diagnosing delirium, and current pharmacological and nonpharmacological therapy options. With a focus on early detection and treatment of delirium, it is hoped that the ensuing complications can be prevented.

WHAT IS DELIRIUM?

The current criteria for the diagnosis of delirium are based on the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV), Text Revision from the American Psychiatric Association.[11] Key diagnostic features of delirium include abnormalities of attention, particularly problems sustaining and shifting attention. In some instances, disturbances such as illusions, delusions, and hallucinations may be seen. Delirium can be categorized as either hyperactive, hypoactive, or mixed. In hyperactive delirium, patients are agitated and restless. Hypoactive delirium is characterized by lethargy, flat affect, and decreased responsiveness. Hyperactive delirium confers a favorable prognosis compared to hypoactive delirium and is often easier to identify.[1]

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Subsyndromal delirium occurs when a patient exhibits one or more symptoms of delirium without fulfilling DSM criteria.[12] It is important to distinguish delirium from agitation, a state of extreme mental and physical activity associated with nonpurposeful movement.[13] Delirium is also separate from psychosis, an altered thinking process without a distinguishable physiologic abnormality.[13]

RISK FACTORS FOR DELIRIUM IN THE CARDIAC SURGICAL INTENSIVE CARE UNIT

The etiology of postoperative delirium is multifactorial resulting from a combination of patient risk factors at admission and perioperative insults.[14] Table 1 summarizes preoperative, intraoperative, and postoperative risk factors.

Preoperative factors

Several studies have looked at severity of illness and incidence of postoperative delirium. Six of seven studies examined by Smith *et al*. showed a positive correlation after surgery.[4] Older age is also considered an independent risk factor for delirium[15] as the incidence of postoperative delirium is diminished in cases of congenital heart operations.[16] The presence of previous brain injury or abnormal neurological findings before surgery was also found to correlate with delirium after surgery. Alzheimer's disease, Parkinson's disease, prior stroke, and transient ischemic attacks (TIAs) may also increase the risk of delirium postoperatively.[16]

Table 1: Causes of delirium in the perioperative period

Preoperative causes	Intraoperative causes	Postoperative causes
Age Disease severity Prior neurological disease (Alzheimers, Parkinson's, prior CVA/TIA) Previous psychiatric disease (major depressive disorder, schizophrenia/ schizoaffective) Substance abuse	Bypass time Surgical complexity Perfusion management (MAP, flow rates, temperature, hematocrit)	Medications (benzodiazepines, steroids, acalcineurin inhibitors) Sleep deprivation Immobility/physical restraints Disease severity (low cardiac output requiring need for mechanical support or prolonged high-dose inotropic/ vasopressor support) Prolonged ICU stay Prolonged mechanical ventilation

TIA: Transient ischemic attack, MAP: Mean arterial pressure, ICU: Intensive Care Unit, CVA: Cerebrovascular accident

Use of psychoactive drugs preoperatively has also been demonstrated to increase the incidence of delirium.[17]

Intraoperative factors

Studies have examined whether length of cardiopulmonary bypass (CPB) contributes to delirium after cardiac surgery and yielded conflicting results. Smith *et al*. reviewed 12 studies pertaining to this question and found six studies where it contributed to postoperative delirium; five found no effect and one study found a negative correlation.[4] The duration of bypass is often dependent on the complexity of the procedure with longer bypass times required for more technically challenging procedures. Kimball and Blachy each independently found that as the complexity of the surgical procedure increased, the risk for postoperative delirium also increased.[18,19] It is believed that this may be due to the increased release of microemboli in complex procedures such as mitral and aortic valve replacement. For coronary artery bypass surgery (CABG), no linkage has been demonstrated between microemboli and delirium.[20]

Type of surgery is also known to influence the incidence of delirium. Valve surgery is associated with a 70% increase in delirium relative to CABG.[21] Delirium rates up to 90% have been reported in operations that required replacement of both the mitral and aortic valves.[19,22] While several studies have suggested that avoiding CPB altogether decreases the incidence of psychiatric and neurological complications postoperatively,[23,24] no difference has been found between on-pump and off-pump CABG.[25,26] For procedures requiring complex aortic reconstruction or deep hypothermic circulatory arrest, the incidence of delirium has been described in a range of 5–30%.[3] Delirium after heart transplantation has been reported to occur between 2% and 9% of cases.[27] There are no reported studies on the incidence of delirium following cases ventricular assist device placement.

Use of high-dose steroids to prevent the systematic inflammatory response during bypass has also been shown in two recent major trials not to have any impact on the incidence or duration of delirium after cardiac surgery.[28] The Intraoperative High-Dose Dexamethasone for Cardiac Surgery trial published in 2012 randomly assigned 4494 patients across 8 cardiac surgical centers to receive a single intraoperative dose of 1 mg/kg dexamethasone and found no statistically significant difference in the incidence of delirium.[29]

The methylprednisolone in patients undergoing CPB trial (SIRS) was published in 2015. In eighty hospital or cardiac surgery centers in 18 countries, a dose of 250 mg of methylprednisolone administered at anesthetic induction and again at initiation of CPB compared to placebo did not yield any difference or reduction in the incidence of delirium.[30]

Neuromonitors commonly used during cardiac surgery such as cerebral oximetry and/or processed electroencephalogram (EEG) monitors (i.e., bispectral index [BIS]) have also proven helpful in predicting postoperative delirium. A total of four studies analyzing cerebral oximetry and its impact on postoperative delirium have been published.[31] However, only one used an objective assessment to monitor delirium in the postoperative period.[32] The authors reported a delirium rate of 27% in that study and found that patients with lower preoperative cerebral saturation or a cerebral saturation of <50% intraoperatively were associated with delirium. Another study demonstrated that intraoperative excursions of mean arterial blood pressure above the upper cerebral autoregulation limit during CPB are associated with risk for delirium.[33] With respect to the BIS monitor, a longer duration of intraoperative EEG burst suppression along with BIS value <20 has been shown to correlate with increased odds of developing delirium.[34,35]

Temperature management during CPB has also been extensively researched in the past 20 years with widely disparate outcomes.[36,37] Unfortunately, the confounding variables of type of cardioplegia (i.e., dextrose-rich), glucose management, and postoperative hyperthermia management make these studies inconclusive when looking for causal relationships to postoperative cognitive events.

The hematocrit level during CPB has also been shown to affect postoperative morbidity. Karkouti *et al*. studied 9080 patients and observed a 10% increased stroke rate for each percentage decrease from a hematocrit of 21%. Other studies have shown that hematocrits under 22–23% on bypass were independent risk factors for neurologic injury.[38]

Postoperative factors

Arenson *et al*. recently completed a retrospective review of >1000 patients who underwent cardiac surgery at a single hospital in Manitoba. Postoperative risk factors associated with in-hospital delirium after cardiac surgery included postoperative stroke or TIA, mechanical ventilation longer than 24 h, the requirement for any transfusion in the postoperative period, and postoperative acute kidney injury.[39]

Postoperative medications can also contribute to delirium in the cardiac surgical ICU. Age-related changes in absorption, distribution, and renal excretion all affect drug metabolism and pharmacokinetics.[40] A recent prospective study that followed 418 cognitively intact elderly patients taking benzodiazepines admitted to the hospital found that these drugs accounted for 29% of the delirium that occurred. Patients were especially at risk if the benzodiazepines were withdrawn while the patient was in the hospital.[41]

Low cardiac output has also been examined as a potential cause of psychiatric abnormalities. It has been shown that patients who demonstrate a low cardiac output during the first several postoperative days experienced hallucinations.[22,24] Interestingly, these symptoms present when a rapid rise in cardiac output occurs. One study showed that the use of an intra-aortic balloon pump (IABP) correlated with an increased risk of delirium. This most likely was related to the increased use of neuroleptics and narcotics to sedate patients with an IABP.[42]

STRATEGIES TO IDENTIFY DELIRIUM

Detection of delirium has substantially improved with the development of scoring methods designed specifically for ICU patients.[43] The American College of Critical Care Medicine guidelines[44] as well as the Society of Critical Care Medicine guidelines[45] recommend routine monitoring for delirium in adult ICU patients stating that early detection and treatment improve outcomes. Valid scoring methods especially designed for ICU patients allow delirium to be detected in both intubated and nonintubated patients even by ICU personnel that have no formal psychiatric training.[46] There are currently a number of assessment instruments for use in ICU patients [Table 2]. However, a recent survey found that only 33% of practitioners use a specific standardized tool for assessing delirium.[47] The use of a standardized method is recommended that the sensitivity of “clinical impression” for detection of delirium is only 29%.[48]

Among the various scoring methods developed for use in ICU patients, the confusion assessment method for

Table 2: Delirium scoring methods validated in Intensive Care Unit patients

Confusion assessment method for the Intensive Care Unit
Intensive Care Delirium Screening Checklist
Neelon and Champagne Confusion Scale
Delirium Detection Score
Cognitive test for delirium
Abbreviated cognitive test for delirium
Nursing Delirium Scoring Scale

the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) were found to be the most valid when compared to the gold standard (DSM-IV criteria) [Table 3] and were also found in 2 meta-analyses to be the most sensitive and specific tools for detecting and monitoring delirium in adult ICU patients.[58,59] In addition, predictive validation of the presence of delirium using these tools was associated with clinical outcomes such as increased ICU and hospital length of stay[60] and mortality.[61]

The CAM-ICU delirium scoring instrument[50] was adapted from the original CAM[62] delirium scoring method to allow for testing of nonverbal mechanically ventilated patients. In 2 meta-analyses, the pooled sensitivity of CAM-ICU was found to be 75.5–80%, and specificity was 95.8–95.9% for detection of delirium.[58,59] No formal psychiatric training is necessary for its use. It uses nonverbal tasks such as picture recognition, vigilance tasks, simple commands, and simple yes/no logic questions to allow for assessment of the four main components of delirium.[63] It should be conducted once or twice daily, and patients are scored as either positive or negative for delirium. No assessment of severity of delirium is possible. In addition, it cannot be used in patients who are heavily sedated. Thus, before screening for delirium, a patient's level of consciousness and sedation should be assessed using a sedation scale such as the Richmond agitation sedation scale.[64]

As opposed to CAM-ICU, ICDSC is an assessment using data collected over time (e.g., a nursing shift) to capture the fluctuation of symptoms required for the diagnosis of delirium.[56] It consists of an 8-item screening checklist based on the DSM-IV criteria and other components found in delirium.[65] An ICDSC score of 4 points or higher exhibited a sensitivity of 99% and specificity of 64% for ICU delirium.[56] In 2 meta-analyses, the pooled sensitivity was found to be 74–80.1% and specificity was 74.6–81.9%.[58,59] ICDSC also can provide an indication of the severity of delirium based on the score.

MANAGEMENT STRATEGIES FOR PREVENTION OF POSTOPERATIVE DELIRIUM

In this section, we highlight the current data on pharmacologic and nonpharmacologic strategies to prevent delirium in cardiac surgical patients.

Pharmacologic

Conventional sedatives used in the care of patients after cardiac surgery include propofol, midazolam, and morphine. Benzodiazepines have been demonstrated to increase delirium in the cardiac surgical ICU[66] and should be used with caution. Opioids have not been shown to influence the incidence of delirium in the cardiac surgical population.[67] Dexmedetomidine, a centrally acting α-2-adrenergic agonist, has gained attention given its ability to provide adequate postoperative sedation and analgesia and demonstrated a lower incidence of delirium after cardiac surgery.[68] In 2009, Maldonado *et al*. randomized patients to receive dexmedetomidine (loading dose = 0.4 μg/kg, infusion rate = 0.2–0.7 μg/kg/h), propofol (25–50 μg/kg/min), or midazolam (0.5–2 mg/h) for postoperative sedation and found that the rate of delirium was significantly lower in patients receiving dexmedetomidine compared to propofol or to midazolam (3% delirium in dexmedetomidine group vs. 50% in propofol group and 50% in midazolam group). These results were corroborated in 2015 when Djaiani *et al*. published the results of a prospective, randomized trial in elderly patients (>60 years old) undergoing cardiac surgery demonstrating a shorter duration of delirium and longer onset till delirium occurrence in patients receiving dexmedetomidine compared to propofol for postoperative sedation.[69] Patients can be safely extubated while receiving dexmedetomidine allowing them to remain sedated and spontaneously breathing while receiving analgesia. The benefits of dexmedetomidine on reducing the incidence of delirium have also been upheld when compared to other commonly used analgesics and sedatives in the ICU such as morphine or remifentanil.[70,71] Ketamine, when administered at a dose of 0.5 mg/kg at the time of induction intraoperatively, has also been shown to decrease delirium related to its ability to serve as an analgesic adjunct to opioids.[7,72]

Data for the use of antipsychotic drugs in mitigating postoperative delirium in cardiac surgical patients are limited. The most commonly used antipsychotic drugs for treating delirium include haloperidol, olanzapine, and risperidone. However, risperidone is the only agent that has been studied in the context of delirium after

Table 3: Validation and reliability studies of confusion assessment method for the Intensive Care Unit and Intensive Care Delirium Screening Checklist

Study	Scoring Method	Delirium prevalence (%)	Study design	Study population	Comparator	Sensitivity (%)	Specificity (%)	Interrater reliability (kappa statistic)
Ely *et al*.[49]	CAM-ICU	87	Prospective, cohort study, single-center	38 medical and coronary ICU patients (58% mechanical ventilation), 293 assessments	Intensivist and 2 intensive care nurses using the CAM-ICU versus delirium expert using criteria from the DSM IV	Intensivist - 100 Nurse 1 - 95 Nurse 2 - 96	Intensivist - 89 Nurse 1 - 93 Nurse 2 - 93	0.81-0.95
Ely *et al*.[50]	CAM-ICU	39	Prospective, cohort study, single-center	96 medical and coronary ICU patients (100% mechanical ventilation), 471 paired daily assessments	2 intensive care nurses using the CAM-ICU versus delirium expert using criteria from the DSM IV	Nurse 1 - 100 Nurse 2 - 93	Nurse 1 - 98 Nurse 2 - 100	0.96
Lin *et al*.[51]	CAM-ICU	22	Prospective, cohort study, single-center	111 medical and coronary ICU patients (100% mechanical ventilation), 204 paired daily assessments	2 research assistants using the CAM-ICU versus delirium expert using criteria from the DSM IV	Assessor 1 - 91 Assessor 2 - 95	Assessor 1 - 98 Assessor 2 - 98	0.91
McNicoll *et al*.[52]	CAM-ICU	50	Prospective, cohort study, single-center	22 elderly medical ICU patients (0% mechanical ventilation), 22 paired assessments	One clinician researcher using the CAM-ICU and one using CAM	73	100	0.64
Pun *et al*.[53]	CAM-ICU		Prospective, cohort study, multicenter	711 medical ICU patients	Bedside nurse versus Reference standard rater	N/A	N/A	0.75 at community hospital, 0.92 at academic hospital
Van Eijk *et al*.[54]	CAM-ICU	41	Prospective, multicenter	181 mixed medical and surgical ICU patients	ICU nurse using CAM-ICU versus delirium expert using criteria from the DSM IV	47	98	N/A
Luetz *et al*.[55]	CAM-ICU	40	Prospective, cohort study, single-center	156 surgical ICU patients	Trained staff members using CAM-ICU versus delirium expert using criteria from the DSM IV	81	96	0.89
van Eijk *et al*.[48]	CAM-ICU and ICDSC	34	Prospective, single-center	125 mixed medical and surgical ICU patients	ICU nurse using either CAM-ICU or ICDSC versus delirium expert using criteria from the DSM IV	CAM-ICU - 64 ICDSC - 43	CAM-ICU - 88 ICDSC - 95	N/A
Bergeron *et al*.[56]	ICDSC	16	Prospective, cohort study, single-center	93 mixed medical and surgical ICU patients (mechanical ventilation not reported)	Intensivist and 2 nurses using the ICDSC versus delirium expert using ICDSC	99	64	0.94
George *et al*.[57]	ICDSC	34	Prospective, cohort study, single-center	59 medical ICU patients (0% mechanical ventilation)	Trained residents using the ICDSC versus delirium expert using the International Classification of Diseases, 10th Revision diagnostic criteria	90	61	0.947

DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, CAM-ICU: Confusion assessment method for the ICU, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, N/A: Not available cardiac surgery.[67] Risperidone acts by antagonizing dopamine D2 and serotonin 5-HT2 receptors and has a half-life that can be up to 20-h long in poor metabolizers with few adverse side effects.[6,72] In a randomized, double-blinded, placebo-controlled study, a single dose of 1 mg sublingually upon regaining consciousness from cardiac surgery demonstrated a reduced incidence of delirium (11.1% vs. 31.7%).[6]

Delirium has also been postulated to occur from a deficiency in the neurotransmitter acetylcholine in the brain.[73] Use of rivastigmine, a cholinesterase inhibitor that is known to inhibit the breakdown of acetylcholine in the neural synapse, is evaluated in a recent randomized, double-blind, prospective interventional study. A 1.5 mg dose of rivastigmine administered the evening before the surgery and every 6 h for 6 days after the surgery was unable to demonstrate a significantly lower rate of delirium.[74] Statins are often recommended preoperatively in cardiac surgical patients given their beneficial effects on outcomes. However, the results of several studies have yielded conflicting results with their ability to reduce delirium and are thus not solely recommended for this purpose.[75-77]

Nonpharmacologic

Recently published clinical practice guidelines are now recommending that nonpharmacologic therapies be considered as "first line" interventions for both prevention and in the management of postoperative delirium.[78] Healthcare teams should implement strategies for the primary prevention of postoperative delirium that involve a multicomponent intervention using an interdisciplinary team. This has reached utmost importance with the inclusion of delirium in the evidence-based ABCDE bundle approach involving awake and breathing coordination (ABC) of mechanically ventilated patients, delirium monitoring, and early mobility, designed to improve functional outcomes in critically ill patients.[79]

In the cardiac surgery patients, utilization of the appropriate history and physical screening and initial diagnostic tests in the preoperative planning phase can prospectively identify patients at high risk for delirium.[39,80-84] Identification of cognitive, substance and alcohol abuse, mood disorders, and frailty in addition to the previously discussed risk factors can be identified in elective patients.[85] This information can be then communicated to the intraoperative and postoperative healthcare teams to assist with targeted surveillance and subsequent management of the patient. Furthermore, this information can allow patients and their families to be better informed of potential delirium risk in the postoperative period.[81]

In the ICU and step-down ward, healthcare teams can implement nonpharmacologic interventions to assist in the prevention of delirium or potentially mitigate delirium if it does occur. Postoperative strategies include the promotion of reorientation (i.e. provide orientation on a regular basis), sleep protocols, early mobility, avoiding restraints, visual and hearing impairment aids, adequate nutrition and hydration, pain management, appropriate medication usage, and adequate oxygenation.[86-91]

Use of sleep protocols

Patients in ICU environment frequently experience markedly disrupted sleep, placing them at increased risk for delirium.[89,92,93] The use of relatively simple nonpharmacologic sleep protocols is recommended to improve delirium in the ICU.[44,92] This includes sleep aids such as earplugs, sleep masks, stress balls (to reduce anxiety/agitation), modification of medications and procedures to allow an uninterrupted period of sleep at night, and implementation of noise reduction strategies.[91,93,94] Recently Kamdar *et al*. have described the effectiveness of a multi-faceted sleep-promoting intervention protocol that included the use of daily reminder checklists for the healthcare team.[95] This protocol includes day/night environmental intervention (e.g., minimizing caffeine, avoiding excessive napping, and dimming lights) and use of nonpharmacologic sleep aids (e.g., ear plugs, sleep mask, and soothing music). Using a step-wise implementation process, the authors demonstrated significant improvements in daily noise ratings and daily delirium/coma-free status (odds ratio: 1.64, $P = 0.03$). The authors have provided further description of their practical multistep process to facilitate other teams with the implementation of a similar process at their center.[88]

Early mobilization

There is increasing consensus that the traditional paradigm of prolonged bed-rest in the ICU contributes to acquired neuromuscular weakness, prolonged hospital length of stay and is associated with increased rates of delirium.[87,96] In 2009, Schweickert *et al*.[88] reported a single-center, randomized control trial of 104 mechanically ventilated patients randomized to either early exercise and mobilization during periods of daily interruption of sedation or to daily interruption of sedation with current standard therapy as ordered by the primary care team. Early mobilization interventions were initiated with passive and active range of motion activity in the supine position and progressed to sit-to-stand transfers, pre-gait exercises and ultimately walking depending on the patient's stability. The authors found that the daily interruption of sedation combined with physical and occupational therapy, from the onset of their critical illness in ICU, resulted in an improved return to baseline functional status (59% vs. 35%, $P = 0.02$) and a significant reduction in ICU length of stay (2 vs. 4 median days, $P = 0.02$) and hospital delirium (28% vs. 41% of total hospital days, $P = 0.01$). The creation of an ICU "Mobility Team" using a protocol that facilitates early physical therapy has been demonstrated to be feasible, safe, and associated with reduced costs.[97]

The delirium toolbox

Rudolph *et al*. have recently described a quality improvement project that was conducted at VA Boston Healthcare System facilities.[90] The authors describe the creation of a "Delirium Toolbox" that includes items to correct sensory input (reading glasses, magnifying glasses, and hearing amplifier), stimulate cognition (jigsaw puzzles, crossword/word search activity, books, playing cards, modeling clay, and stress balls), and promote sleep (earplugs, eye masks, and headphones). These items were chosen because of their correlation with modifiable delirium risk factors.[90,98] Using a propensity-matched analysis of 566 patients, the authors demonstrated the use of their "toolbox" was associated with lower hospital lengths of stay, restraint use, and variable direct costs. This study, however, was performed in a nonsurgical acute care ward and hence further analysis was required to determine the effectiveness in a postcardiac surgery in-patient ward.

Evidence of effective nonpharmacologic interventions

Previous reports and recently published clinical practice guidelines have stated that adherence to a nonpharmacologic multicomponent intervention strategy resulted in a "dose-response" such as reduction of rates of delirium.[78] However, the strong recommendations contained in these guidelines are largely informed by moderate levels of evidence from both surgical and nonsurgical patient populations. Interestingly, Al-Qadheeb *et al*. recently reviewed 17 trials enrolling 2849 patients that evaluated either a pharmacologic intervention ($n = 13$), a multimodal intervention ($n = 2$) or a nonpharmacologic intervention ($n = 2$). The authors found that while there was an overall reduction in delirium duration in the intervention groups (−0.64 days, $P = 0.01$), they were unable to demonstrate a reduction in mortality. Therefore, while it is unlikely that nonpharmacologic intervention is harmful, there is still an urgent need for further study of effectiveness in postoperative delirium in the cardiac surgery patient.[99]

CONCLUSION

Delirium remains a frequent manifestation in the cardiac surgical population and contributes to increased morbidity, mortality, and resource utilization. While many studies have identified risk factors and strategies to identify delirium, the ideal treatment strategy has yet to be determined. Future studies are needed in the cardiac surgical population to define better the optimal approach to managing delirium after cardiac surgery.

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