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Delirium in the Cardiac Surgical Intensive Care Unit

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Abstract

Purpose—Evidence is emerging that delirium is associated with both short- and long-term morbidity and mortality. This review highlights the epidemiology, outcomes, prevention and treatment strategies associated with delirium after cardiac surgery.

Recent findings—The incidence of delirium after cardiac surgery is estimated to be 26-52%, with a significant percentage being hypoactive delirium. It is clear that without an appropriate structured test for delirium, the incidence of delirium will be under-recognized clinically. Delirium after cardiac surgery is associated with poor outcomes including increased long-term mortality, increased risk of stroke, poor functional status, increased hospital readmissions, and substantial cognitive dysfunction for 1-year following surgery. The effectiveness of prophylactic antipsychotics to reduce the risk of delirium is controversial, with data from recent small studies in non-cardiac surgery potentially showing a benefit. Although anti-psychotic medications are often used to treat delirium, the evidence that anti-psychotics in cardiac surgery patients reduce duration of delirium or improve long-term outcomes following delirium is poor.

Summary—Clinicians in the ICU must recognize the impact of delirium in predicting long-term outcomes for patients. Further research is needed in determining interventions that will be effective in preventing and treating delirium in cardiac surgical setting.

Keywords

delirium; cognitive dysfunction; cardiac surgery

Introduction

Post-cardiac surgery delirium is both a common and costly complication in the cardiac surgical intensive care unit (ICU). Depending on the methodology, estimates of incidence have ranged from 3-70%, with best estimates using rigorous methodology likely between 26-52%.[1-4] The potential consequences of delirium after cardiac surgery include increased morbidity,[5] decreased functional status,[1] cognitive decline,[6] and increased long-term mortality.[7] Because delirium may be preventable, attention has turned to delirium as a potential marker of patient safety and quality of care.[8] Although much research has focused on improving the management of delirium in general ICU populations, specific studies are

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needed to translate these findings into improved management of delirium in the cardiac surgical ICU.

Definition and Diagnosis

The current criteria for diagnosis of delirium are based on the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) from the American Psychiatric Association.[9] Key diagnostic features of delirium include: acute onset and fluctuating course, inattention, impaired consciousness, and disordered cognition. Three subtypes of delirium have been described but are not well-defined—hyperactive, hypoactive, and mixed subtypes.[10] Hypoactive delirium may predominate in the cardiac intensive care unit, with a recent finding of the hypoactive subtype accounting for 92% of delirium cases in a mixed medical/surgical cardiac intensive care unit.[11] Subsyndromal delirium occurs when a patient exhibits symptoms of delirium without fulfilling DSM-5 criteria, and subsyndromal delirium has also been associated with poor outcomes.[12]

Delirium is difficult to diagnose in the ICU and the majority of delirious patients may not be recognized.[13] Although more than 24 delirium instruments have been used in published studies,[8] the most widely used instrument is the Confusion Assessment Method (CAM), which has a sensitivity of 94% and specificity of 89% against a gold standard of psychiatrist diagnosis.[14] The CAM-ICU was developed to accurately diagnose delirium in intensive care unit patients, who are often nonverbal due to mechanical ventilation.[15] The CAM-ICU has been estimated to have a sensitivity of 95% and specificity of 89%. In order to accurately use both CAM and CAM-ICU, formal training methods are recommended. Importantly, CAMICU is likely not sensitive for the diagnosis of delirium in non-critically ill hospitalized patients[16] or in patients in the post-anesthesia care unit.[17] In addition, diagnosis of delirium through billing codes or nurse estimates of delirium without a structured examination has poor sensitivity, although a chart review method has been validated with a sensitivity of 74%.[18,19]

Causes

The development of delirium is thought to be multifactorial, likely resulting from a combination of patient vulnerability and perioperative insults.[20] According to this framework, the development of delirium in healthy patients might require a significant noxious insult, while in a vulnerable patient, only a relatively benign insult might be required. Indeed, in a long-term study of the effect of delirium on mortality after cardiac surgery,[7] the effect of delirium was most pronounced in younger patients, indicating that delirium may be a particularly ominous sign in more robust patients.

To assess baseline vulnerability, the most widely used prediction rule for delirium after cardiac surgery was developed and validated by Rudolph et al. in 2009,[2] and includes four items: prior stroke/transient ischemic attack, Geriatric Depression Scale>4, abnormal albumin, and Mini-Mental State Examination (MMSE) score. Importantly, the factors derived from this prediction rule highlight the potential importance of cerebral atherosclerosis in the pathogenesis of delirium.[21] In support of this hypothesis, a recent study demonstrated that the presence of severe white matter hyperintensities on baseline

MRI (a marker of cerebrovascular disease) was associated with a 3.9 fold increase in the odds of delirium after cardiac surgery (95% CI 1.2-12.5).[22,23] Another measure of cerebrovascular disease, low baseline near infrared spectroscopy level, has also been associated with the development of postoperative delirium.[3]

In addition to baseline patient vulnerability, perioperative insults that might contribute to delirium in the post cardiac surgery period are common. Both the choice of sedative and the levels of sedative have been widely implicated in increasing delirium risk in both medical and surgical settings.[24-26] Maintaining adequate blood pressure may be also be important, as evidence has emerged of an association between inadequate cerebral perfusion and the development of postoperative delirium.[27] Similarly, in a small study of patients, impaired cerebral autoregulation was associated with sepsis-related delirium. [28] Breakdown of the blood-brain barrier has long been hypothesized to result after cardiac surgery. In a recent examination of MRI data in patients after on-pump and off-pump cardiac surgery, 47% of patients had enhancement of CSF on MRI FLAIR images, a marker of blood-brain barrier disruption. Further research is needed to determine how disruption of blood brain barrier might contribute to postoperative delirium.

In spite of general knowledge of risk factors for delirium, the precise pathophysiology of delirium is not well known, although it is thought that overlapping biologic factors, rather than a single mechanism, are responsible for the onset of delirium.[8] Potential mechanisms for delirium onset include increased inflammation,[29] changes in neurotransmittors (especially acetylcholine[30]), electrolyte and metabolic disorders,[31] hemodynamic changes,[27] and genetic factors.[32] The neuroinflammatory state may play a key role in the development of postoperative delirium. High baseline levels of cortisol[4,33] and IL-6[4] were recently shown to be increased in patients with delirium, after cardiac surgery. An emerging body of data has also linked microglial activation with postoperative delirium. In the elderly and in patients with neurodegenerative disease, microglia are primed to exhibit a more robust pro-inflammatory response to stimuli, potentially leading to an exaggerated CNS inflammatory response and subsequent delirium in the setting of cardiac surgery.[34-36]

Consequences

The long-term consequences of delirium are an area of active investigation, with emerging evidence indicating that delirium may contribute to long-term cognitive decline in both medical and surgical patients.[37-39] The effect of delirium on cognitive decline in patients undergoing cardiac surgery appears to be similar. Recently, Marcantonio et al. followed 225 patients using the MMSE to determine the effect of delirium on cognitive change.[6] Patients who experienced delirium had lower MMSE scores at one month (24.1 vs. 27.4; $p<0.001$) and one year (25.2 vs. 27.2; $p<0.001$), and more patients with delirium had not returned to their preoperative baseline cognitive level at 6 months (40% vs. 24%; $p=0.01$), with a trend at one year (31% vs. 20%; $p=0.055$). These results imply that patients who develop delirium after cardiac surgery may experience cognitive decline with prolonged impairment. Recent evidence has also emerged that patients who undergo hospitalizations complicated by critical illness may suffer from long-term cognitive decline.[40,41] The dramatic extent of cognitive decline in patients was demonstrated by a recent study which followed patients for

a year after admission to a mixed medical/surgical ICU with respiratory failure or cardiac or septic shock.[42] Results from this observational study showed that at 12 months, up to a third of patients had cognitive scores similar to patients with moderate traumatic brain injury or mild Alzheimer's disease.[42] Importantly, development of delirium may have interactions with critical illness, since a longer duration of delirium was independently associated with worse global cognition and executive function at 3 and 12 months (all p values <0.05).

In addition to cognitive status, postoperative delirium has been associated with functional decline at 1-month following cardiac surgery and a trend towards decreased function at one year.[1] Quality of life may also be affected by delirium. In a prospective study of 300 cardiac surgery patients, postoperative delirium was independently associated with lower scores in 7 of the 8 domains of the SF-36, a validated measure of quality of life. [43] Long-term mortality was also significantly higher in the patients with delirium, an observation that is supported by the results of several other studies in the cardiac surgery population.[5,7]

Prevention

Both non-pharmacologic and pharmacologic methods may be used to prevent delirium.

Non-pharmacologic

In randomized trials in the medical ICU setting, early mobilization has been shown to reduce days of delirium.[44,45] Using this evidence, the recent "Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit" recommend early mobilization whenever feasible to reduce delirium.[46] Further supporting this recommendation is an observational study in the cardiac surgical ICU, which demonstrated that immobilizing factors were independently associated with postoperative delirium.[11] However, the evidence for the effectiveness of early mobility to reduce delirium specifically in the cardiac surgical ICU is lacking. The ICU environment has been hypothesized to contribute to the development of postoperative delirium through such factors as poor sleep quality, lack of natural light, and increased ambient noise.

However, in a prospective study of cardiac surgery patients in windowless non-private rooms vs. patients in private rooms with windows, there was no difference in the incidence of postoperative delirium,[47] suggesting that the postoperative environment either does not play a substantial role in the onset of delirium in the post cardiac surgery setting or needs to be assessed using different methodology. A recent meta-analysis also failed to find a single study demonstrating benefit of pre-admission interventions to prevent delirium after cardiac surgery.[48]

Generally, primary prevention using non-pharmacological methods is an effective strategy for delirium in the general hospital setting. In non-ICU settings, the most widely known primary prevention strategy with good evidence of delirium reduction is the Hospital Elder Life Program (HELP),[49] a multicomponent intervention which includes strategies on reorientation, reduced use of psychoactive drugs, early mobilization, sleep promotion, optimal hydration, and use of hearing/visual aids. Similarly, proactive geriatric consultation

may reduce delirium.[50] However, neither of these non-pharmacologic methods has been adequately studied in the cardiac surgical ICU.

Pharmacologic

The ability of prophylactic antipsychotic agents to reduce delirium incidence is controversial, and recent guidelines from the Society of Critical Care Medicine provide no recommendation for using either haloperidol or atypical antipsychotics to prevent delirium in the ICU. However, two recent randomized controlled trials in non-cardiac surgery ICU patients show a reduction in the incidence of delirium with prophylactic haloperidol administration, in all patients[51] and in patients at high risk for delirium.[52] In cardiac surgery patients in particular, a small study suggested that sublingual risperidone might reduce the incidence of delirium.[53] In non-ICU patients, the results of prophylactic administration of antipsychotic agents have been mixed,[54,55] although two recent meta-analyses did find a modest reduction in the incidence of delirium with prophylactic antipsychotic administration.[56,57] Large randomized trials in cardiac surgical patients are needed to confirm the benefits of prophylactic antipsychotic administration.

There are conflicting results on the effect of preoperative statins on the incidence of delirium. In a prospective study using CAM-ICU to measure delirium after cardiac surgery, there was no difference in delirium according to statin use, although, the incidence of delirium was also low (3%).[58] However, in another prospective study of cardiac surgical patients, with an incidence of delirium of 11.5%, preoperative statin use was associated with a reduced incidence of postoperative delirium.[59] All of the studies were limited by the observational study design and low rates of delirium. Further studies to determine the effects of statins of delirium are needed given the increasing prevalence of statin use in cardiac surgery patients. The anti-inflammatory effects of dexamethasone (1mg/kg) vs. placebo were recently investigated in a large randomized controlled trial of cardiac surgery patients, with no difference in the primary outcome of 30-day major adverse events.[60] The rate of delirium (as measured by neuroleptic administration) was slightly lower in the dexamethasone arm (9.2%) compared to placebo (11.7%; p=0.006), although the difference was small and the results are limited by imprecise delirium measurement and recording of delirium as a secondary outcome.

Although cholinergic deficiency has been hypothesized to contribute to delirium, acetylcholinesterase inhibitors have not been shown to reduce post-cardiac surgery delirium,[61] and may actually increase mortality.[62] A small study in cardiac surgical patients showed a potential reduction in postoperative delirium when ketamine (0.5mg/kg) was used as an adjunct agent for induction of anesthesia, but these results have not been replicated.[63]

Sedation regimen may impact postoperative delirium and incidence. Although data supporting the association between opioids or benzodiazepines and delirium have been varied, it is generally thought that both classes of drugs (especially the latter) increase the risk of delirium, with benzodiazepine use being independently associated with delirium in the cardiac ICU.[11] Two randomized trials in predominantly medical ICU patients reported reduced incidence of delirium in patients randomized to dexmedetomidine vs. benzodiazepines.[25,64] In cardiac surgery patients, there is evidence from two small

randomized trials that dexmedetomidine may reduce the incidence[65] or duration[66] of postoperative delirium. However, a meta-analysis found no evidence of a beneficial effect of dexmedetomidine as a sedative agent on the incidence of delirium.[67] Critical care guidelines provide no recommendation for the use of dexmedetomidine to *prevent* delirium in the surgical ICU.[46]

Therapy

The primary goals of managing patients with delirium are to treat and remove potentially reversible precipitating factors, and to ensure patient safety. Medications should be reviewed to determine delirium-causing potential. Although haloperidol is commonly used in delirious patients and can reduce agitation symptoms, it is controversial whether antipsychotic agents meaningfully reduce the duration of delirium,[8] with a recent systematic review citing severe methodological limitations of the majority of studies addressing this question.[68] Several systematic reviews found no difference between typical and atypical antipsychotic agents in reducing duration of delirium in general medical and surgical patients.[69,70] However, a small randomized trial of a mixed medical/surgical ICU population did find that quetiapine vs. placebo (in addition to haloperidol as needed) resulted in reduced duration of delirium.[53] Based on this data, guidelines from the Society of Critical Care Medicine cite that there is no evidence that treatment with haloperidol reduces the duration of delirium, while suggesting that use of atypical antipsychotic agents may reduce duration of delirium.[46] This recommendation evolved from prior guidelines which recommended haloperidol as the preferred agent for the treatment of delirium in critically ill patients.[71] There are generally fewer extrapyramidal side effects (Parkinsonism, dystonia, and akathisia) with newer antipsychotic agents compared to haloperidol, but they can cause more sedation. They should be used cautiously in patients at risk for torsades de pointes.[72] The effectiveness of ondansetron compared to haloperidol to treat delirium was investigated in a small study in cardiac surgical patients, and showed no difference in delirium resolution, but the study was small and underpowered.[73] Rivastigmine should not be used to treat delirium based on evidence of potential harm.[62]

It is unclear how to manage patients with sub-syndromal delirium, who are at high risk for progression to delirium and for poor outcomes.[12] A recent study evaluated risperidone (0.5 mg every 12 hours) for post-cardiac surgery patients with subsyndromal delirium and found that the risk of progressing to delirium was significantly lower in the group randomized to risperidone (14%) vs. placebo (34%), with no differences in side effects.[74]

Conclusion

Delirium is a frequent occurrence in the cardiac surgical ICU and results in increased morbidity and mortality. Research in medical and non-cardiac surgery ICU patients have identified risk factors and management strategies for delirium. Further studies are needed to examine these strategies in the cardiac surgical ICU.

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Key Points

- Delirium is common in the cardiac surgical ICU, and is associated with increased morbidity and long-term mortality.
- Delirium after cardiac surgery may be associated with long-term cognitive decline.
- Interventions that have been effective to prevent and treat delirium in non-cardiac surgery patients need to be studied in the cardiac surgery setting.
- There is conflicting evidence whether prophylactic anti-psychotic administration can reduce the incidence of delirium and whether antipsychotic administration reduces the duration of delirium.